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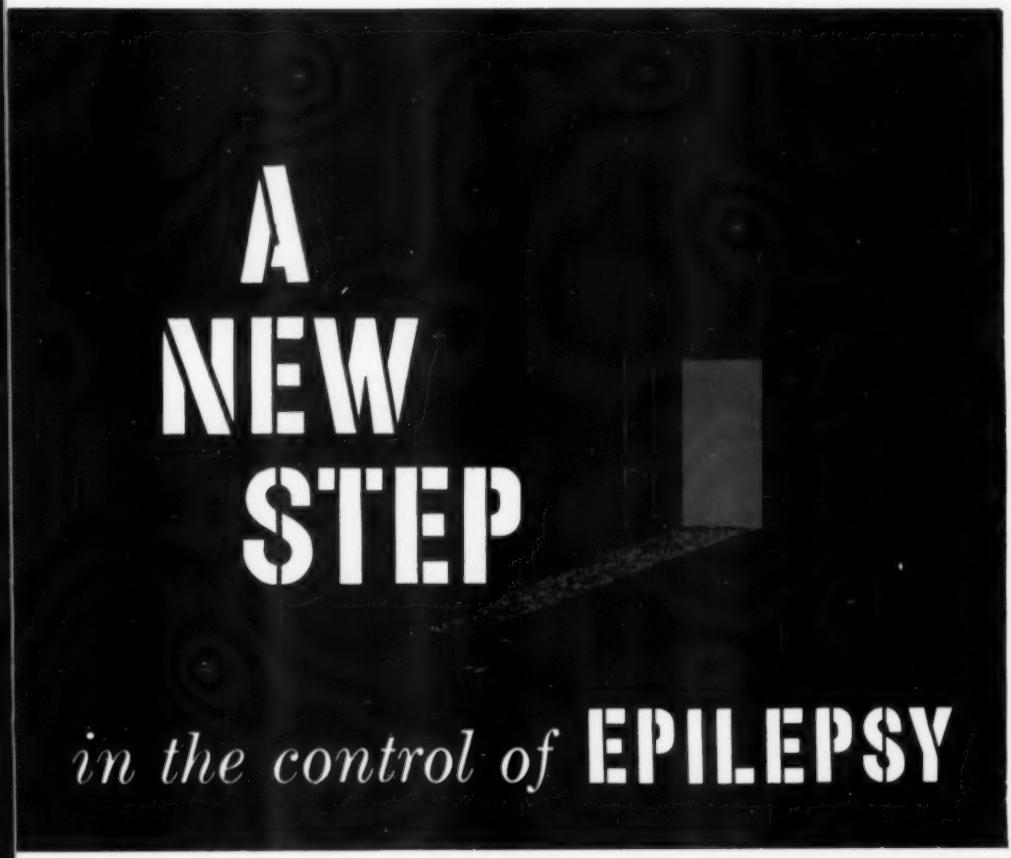

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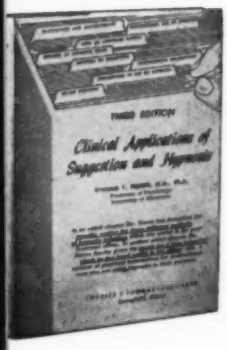

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Predictability of the Electroencephalogram in People with Seizures

STEWART RENFREW, M.R.C.P.; ISABELLA HAGGAR, and MARGOT WATSON, Glasgow, Scotland

Introduction

When electroencephalography is used as a diagnostic test in persons with seizures, it is open to two criticisms. First, markedly abnormal interseizure records are often found in patients who have mild seizures, while, on the other hand, slightly abnormal and normal records are often found in patients who have severe seizures. Consesequently, electroencephalograms afford no evidence of the severity of seizures and vice versa. Second, in patients with seizures an abnormal record can rarely be used with confidence as evidence of organic cerebral disease. This second criticism can still be maintained when the EEG abnormalities are focal, for the clinician reasonably refuses to be satisfied with an electrical focus from which an abnormal histological lesion cannot be inferred with confidence.

The first criticism rests on a distinction which is usually drawn between severe and mild seizures in terms of the violence of convulsions and the depth and duration of unconsciousness. However, a distinction can be drawn between people with seizures in terms of frequency of seizures, the age of onset, and the duration of the condition. In this paper an investigation will be described the results of which strongly suggest that an assessment of seizures based on these variables, together with the type of seizures, does, in fact, correlate well with the EEG findings. Indeed, the correlation is sufficiently close to permit the correct prediction of normal and markedly abnormal records in the majority of patients. It will be shown that some errors of prediction turn out to have a significance which partially invalidates the second criticism.

Received for publication Aug. 31, 1956.

From the Department of Electro-Encephalography, the Glasgow-Royal Infirmary.

Consultant Neurologist (Dr. Renfrew), and recordists (Misses Hagger and Watson), the Glasgow Royal Infirmary.

Method

An initial study was made of 180 consecutive patients past the age of 16 years who had been referred for an EEG because of a complaint of seizures. Information abstracted from their case records was tabulated under various headings, among which were the age of onset, duration of condition, and type and frequency of seizures. Examination of this table revealed that a close correlation did not exist between one variable and the EEG, and that only by combining the variables could such a correlation be demonstrated. The most convenient way of combining the variables was to give patients a score on the basis of each variable, and then to add the four scores. The scoring system eventually adopted was arrived at by trial-and-error method.

Of the original 180 patients, 100 had been seen by one of us (S. R.) at an outpatient clinic, and these were retained in the series. The rest were excluded, since the accuracy of the histories could not be vouched for. Another 400 consecutive patients past the age of 16 years (the histories of all of whom were verified by us) were added, giving a total of 500 patients in the series. During the period in which these 400 patients were studied no reason was found for altering the scoring

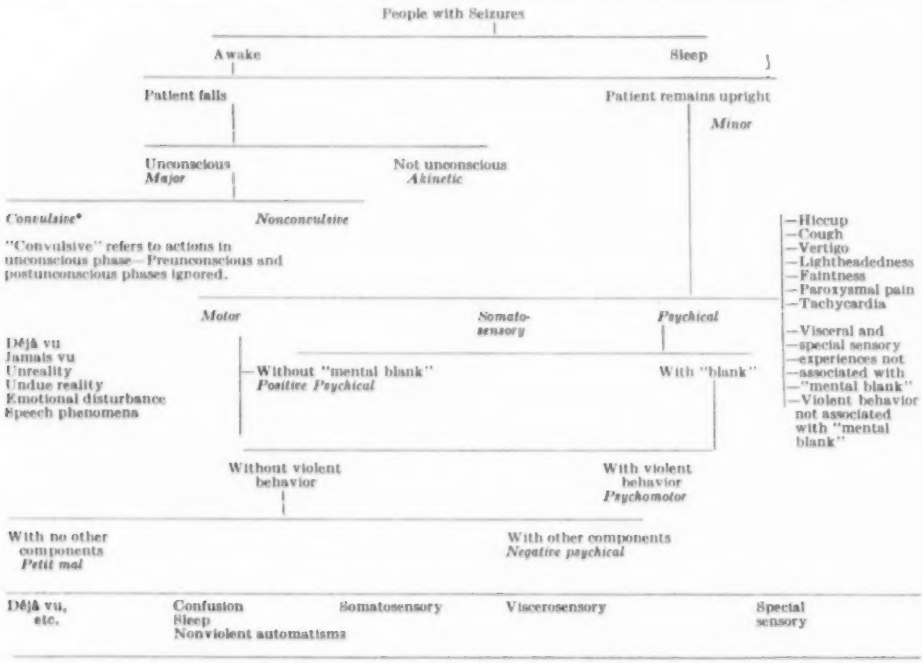
system, and the EEG appearances in terms of "Normal" and "Markedly abnormal" were, in fact, predicted before the recordings were made. When the predictions were inaccurate—and this occurred with only a small minority of patients—the histories were rechecked, as a result of which a few patients were given a new score. Experimenters inevitably have a bias of being more critical of evidence which conflicts with their experimental hypothesis than of evidence which confirms it, the direction of the bias depending on their belief or disbelief in the hypothesis. Belief may be the product of reason in the early stage of an experiment; but belief or disbelief cannot be for long resisted, and the further collection of evidence is biased by this belief. Bias is therefore inescapable, and the only course open to the experimenter is, by conscious effort, to minimize it.

Classification of Patients with Seizures

Types of Seizures.

The division of patients with seizures into classes is fairly orthodox (Chart). There are, however, one or two innovations. The defining properties which distinguish members of the two classes of seizures called major and minor are unequivocal, for in the major class the patient falls and in the minor he remains upright. The class with major seizures is divided into two subclasses on the basis of the loss or presence of consciousness, and the former class is divided on the basis of the absence or presence of convulsions. Any involuntary action whether of somatic or visceral musculature, is covered by the term convulsion, and also included is a spasm of muscle generally described as the tonic phase of a seizure. The important point is that it is only the movement or spasm which occurs during the unconscious phase of a seizure that is regarded as significant in the present investigation, and movements or any other phenomena during the preunconscious or postunconscious phase are ignored. Thus, in the class called "major nonconvulsive" the usual distinctions made by medical au-

Classification of People with Seizures for the Purpose of Predicting EEG's



Blank means a period of amnesia from the subjective point of view and a period of unresponsiveness from the objective point of view.

thors in terms of aura and sequela are disregarded. The description of major seizures requires no further elaboration except, perhaps, to mention that the shivering and trembling often exhibited by a patient recovering consciousness is considered to belong to the postunconscious phase. It should be mentioned that sleep seizures are always convulsive, although this, no doubt, arises from the fact that in sleep seizures it is only convulsions which can be observed.

There are a great variety of minor seizures. A large number of these pass under such names as hiccup, vertigo, lightheadedness, recurrent pain, and tachycardia, to name only a few. Patients with such seizures are excluded from the present investigation, since it is our experience that a markedly abnormal EEG is a rarity in this group. If normal records were predicted in these patients, most predictions would be correct, a result which would scarcely merit mention in this paper.

There are three classes of people with minor seizures, signified by the terms motor, somatosensory, and psychical. The first two, which include myoclonus, need no explanation. Psychical seizures, however, must be described at some length. A feature of some psychical seizures is the patient's unawareness of his surroundings, and this may be described simply as a mental blank, or as an "absence," to use the French name. During the blank the patient cannot be aware that he is having a seizure; else, there would be a contradiction in terms, but he may be aware immediately after he passes through a blank phase that it has occurred. Strictly speaking, it amounts to a period of amnesia. The patient indeed realizes that he has had a mental blank by noticing, for example, that he has missed a portion of conversation, or that people are looking at him as if he had behaved strangely. Occasionally the patient may be aware that he has had a blank without being able to account for this awareness. A witness may observe that during the blank the patient is out of touch with his surroundings, that he looks dazed, and that he does not respond to questioning. From this unresponsiveness it may be inferred that the patient is having a mental blank, so that a mental blank can stand as a defining property whether or not information is obtained from a witness or from the patient himself.

The class of patients with seizures called psychical is divided into two subclasses on the basis of the mental blank. When there is no mental blank, the patient describes psychical experiences which can be put under the headings of déjà vu, jamais vu, disturbances of the sense of reality, and emotional disturbances, such as ecstasy and fear. This class can be called positive psychical. In such seizures a witness may observe nothing abnormal, owing, perhaps, to the brevity of the seizure. The class in which a mental blank occurs is divided into two subclasses on the basis of violent activity. When the patient exhibits violent physical activity, the seizure is called psychomotor, and, in our experience, the interseizure EEG of this kind of patient is always normal.

The class in which there is a mental blank but no violent activity is divided into two subclasses. In one there are no other components beyond a little fluttering of the eyelids and fumbling of the hands. Petit mal is reserved for this class. Should a mental blank last longer than 30 seconds, or should automatisms other than a mild fumbling of the hands occur, the patient is put into the class called negative psychical, in which a variety of components, shown in the Chart may occur. A feeling that a blank is about to occur is sufficient to put the patient into this class, for in petit mal the patient has no warning of an attack. It is worth emphasizing that visceral and special sensory symptoms in the absence of a mental blank are not called psychical seizures. Whether a patient has a positive or a negative psychical seizure is of no importance from the point of view of the EEG, since temporal lobe foci are found equally in the two types. The classification, however, throws

emphasis on the mental blank which, to us, seems a fundamental point when seizures are discussed in relation to the EEG.

There is one kind of psychical seizure which deserves special mention. In this there are disturbances of speech, which may or may not be associated with a mental blank. The patient may say words out of context with a conversation, or he may say words, out of the blue as it were, which are nonsensical. For example, one patient crossed the street to say to a stranger, "You'll hang for this." Of this he later had no recollection. The same patient may say different things at different times. The speech may be gibberish, may consist of some interjectional phrase, such as "Oh my; oh my," or may consist of nonsense words, such as "tick-tock; tick-tock." On occasion the patient may be unable to get words out, or he may have a desire to speak nonsense without doing so, or he may have auditory hallucinations in the form of conversations. Sometimes the speech may be accompanied by gestures normally associated with speaking. These seizures are related to temporal lobe foci in the EEG. Their particular importance wih regard to the EEG is that they are exhibited by many patients, and are often overlooked if the physician does not pose suitable questions to patient and witness.

It is apparent that an analysis of seizures may allow a patient to be put into several classes. For example, one seizure may have psychical, major convulsive, and psychomotor components. In these circumstances the patient can be given several scores on the basis of the type of seizure. The rule was thus made that when a patient had more than one kind of seizure, or when his seizures could be analyzed into different components, he was given a score for each kind on the basis of frequency, age of onset, and duration, and the highest score was the one adopted for that patient. An example given later will make this clear.

The scores for the seizure types are as follows:

Major convulsive	60	Major nonconvulsive	0
Sleep seizures	60	Minor motor and somatosensory	0
Positive and negative psychical	60		
Petit mal	60	Psychomotor	0

Frequency of Seizures.

The total number of seizures a patient may have in a specified period of time, or the average number within a specified period of time, was found to have no significance. The significant point was the period of freedom from seizures. On this basis, a patient was scored for a frequency of one seizure a week if in the past month he had not had a clear week's freedom. Similarly, he was scored for a frequency of one seizure a month if in the past year he had not had a clear month's freedom. If he had a clear month's freedom, he was scored for a frequency of one seizure a year. The scores are as follows:

One or more seizures a week	60
One or more seizures a month	12
One or more seizures a year	0

Age of Onset.

It was not unexpected that the score for the age of onset should be in inverse proportion to the age. That is to say, the earlier the onset the higher the score. It was found by trial and error that the score for age of onset should be calculated as 2(25−age of onset). Should the seizures have begun after the age of 25 years, the patient was given a zero score. The age of onset was taken as the age after which the patient did not have a clear year's freedom from seizures. Thus, seizures at an early age were ignored if they were followed by a remission for more than a year.

Duration of Condition.

This score seemed to act as a correction factor for patients whose seizures began about the age of 16 or 17 years. The score was found to be −(20−duration of condition). If the patient had had seizures for 20 years or more without a year's remission, he was given a zero score.

Final Score.

The final score is given as follows:

2(25−age of onset)−(20−duration of condition)+type of seizure+frequency of seizures

Scoring Groups and the EEG

The initial study of 180 patients indicated that with a score below 75 a normal EEG could be predicted, whereas with a score above 75 an abnormal EEG could be predicted. Some examples can now be given.

(*a*) A patient aged 30 (or any age over 25 years) had major nonconvulsive seizures, beginning within the past year and occurring once a month.

Score: 0—20+0+12=—8. Normal record predicted.

(b) A patient aged 30 (or any age over 25 years) had major convulsive seizures, beginning within the past year and occurring once a month.

Score: 0—20+60+12=52. Normal record predicted.

(*c*) A patient aged 30 (or any age over 25 years) had major convulsive seizures, beginning within the past year and occurring once a week.

Score: 0—20+60+60=100. Abnormal record predicted.

(*d*) A patient aged 30 had major convulsive seizures beginning at the age of 10 years and occurring once a month.

Score: 30—0+60+12=102. Abnormal record predicted.

(*e*) A patient aged 21 years had psychical seizures, beginning at the age of 12 years and occurring once a month.

Score: 26—11+60+12=87. Abnormal record predicted.

(*f*) A patient aged 26 years had major convulsive seizures, beginning at the age of 8 years and occurring once a year, and also psychical seizures, beginning at the age of 24 years and occurring once a month.

Scores: 34—2+60+0=92. 2—18+60+12=56. Abnormal record predicted on the basis of the major convulsive seizures.

An obvious criticism of the scoring system is that not infrequently it cannot be decided with confidence whether a patient is having major convulsive or major nonconvulsive seizures. This is admitted; but if the above examples are examined, it will be seen that should the patient be past the age of 25 and his seizures occur once a month he will have a normal score whether or not his seizures are convulsive. If the seizures occur once a week, the kind of seizure is important; but with this frequency it is not difficult to get an accurate description of the seizures. When the patient is under 25 years of age, the kind of seizure is important, even with a frequency of once a month; but when seizures start in childhood or adolescence, it is not difficult to get an adequate description of the seizures. In summary, on those occasions when it is difficult to get an adequate history, it is found that from the point of view of predicting the EEG the kind of seizure is not important. It is, of course, impossible to obtain a description of all the seizures a patient may have; but if at least one is convulsive, the patient is scored for this unless there is definite evidence that some of the seizures are nonconvulsive. When a witness is sufficiently observant to draw a distinction between convulsive and nonconvulsive seizures in the one patient, he is generally able to give an assessment of the relative frequency of the two kinds. There is no difficulty in scoring when nonconvulsive seizures occur in a phase of the history prior to the major convulsive seizures.

When seizures begin after the age of 25 years, the scoring can be simplified to type and frequency of seizure. Thus, with psychical or major convulsive seizures occurring once a week the patient should have an abnormal EEG. In all other circumstances he should have a normal EEG.

All the remarks made with regard to scoring have one reservation. It has been found that a small number of patients with a normal score have an abnormal EEG within the week following a major convulsive or psychical seizure, although thereafter the EEG returns to normal. When an abnormal EEG was obtained in this way, the procedure was always repeated a clear week after a seizure, and the judgment as to whether a prediction was right or wrong was based on this second EEG. When the frequency is once a week, the time interval between the recording and the seizure is not relevant to the present scoring system. It may be added that in our experience an EEG which is otherwise normal may occasionally be abnormal a few hours prior to a seizure.

TABLE 1.—*Distribution of Patients in Scoring Groups*

Scoring Groups	Major Convulsive	Major Non-convulsive	Psychical Positive and Negative	Sleep	Minor, Motor, and Sensory	Petit Mal	Psychomotor	Total Patients in Each Scoring Group
Below 0	—	43	—	—	16	—	1	60
1= 9	—	15	—	—	7	—	2	24
10= 19	—	8	—	—	2	—	1	11
20= 29	—	6	—	—	4	—	—	10
30= 39	—	3	—	—	—	—	—	3
40= 49	98	9	1	18	9	—	—	135
50= 59	57	12	8	3	1	—	—	81
60= 69	36	1	2	—	3	—	—	42
70= 74	14	4	3	2	1	1	—	25
75= 79	2	1	2	1	2	—	—	8
80= 89	10	1	1	1	—	—	—	13
90= 99	6	—	1	—	—	1	—	8
100=109	12	—	18	1	1	1	—	33
110=119	5	1	10	1	1	—	—	18
Above 120	12	—	12	2	—	3	—	29
Total	252	104	58	29	47	6	4	500

We have the impression that the duration of individual seizures has a part to play in the correlation of the history and the EEG. Unfortunately, duration can rarely be estimated accurately. Nevertheless, it would seem, for example, that psychical seizures which are relatively brief are associated with relatively mild EEG abnormalities, provided, of course, that they are sufficiently frequent and long standing.

Electroencephalograms.

EEG's were recorded on an eight-channel Ediswan apparatus coupled to an analyzer. The recordings were bipolar, and standard electrode placements were used. The majority of EEG's were classified as "normal" and "markedly abnormal," a small number being classified as "slightly abnormal." The slightly abnormal EEG's were of a type found in people without neurological complaints and should properly have been included in the normal group. The criteria adopted for the classification of EEG's were orthodox, although we deviated a little from standard practice, since our control subjects consisted of hospital patients who did not have nervous disease. A control group selected in this way shows more "slightly abnormal" EEG's than a control group selected from the nonhospital population, and, as a result, we have a bias toward describing EEG's as normal rather than abnormal, a bias which may be described as "underinterpreting" records. Control subjects from a nonhospital population are difficult to obtain and are not altogether satisfactory, since, being volunteers, such subjects are self-selected and the selection is therefore not random. The only provocative method used was hyperventilation, and the effects of this were ignored unless wave-and-spike activity was produced. We consider it impossible to define limits of normality with regard to the effects of hyperventilation under the conditions of routine EEG practice.

Results

Table 1 shows the distribution of patients in scoring groups. It is evident that of the 500 patients, about 400 have normal scores. As would be expected, the lower scoring groups are occupied by patients who are scored for major nonconvulsive, minor motor and somatosensory, and psychomotor seizures. As a guide to the reader, it may be said that patients with scores over 100 generally have major convulsive or psychical seizures once a week, whereas patients with scores between 75 and 100 have had seizures since childhood or adolescence, occurring once a month or less. The groups scoring above 75 are equally occupied by patients who have major convulsive and psychical seizures. It should be remembered in this connection that some patients have more than one type of seizure, although they are scored only for the type which gives them the greatest score. Consequently, more than 58 patients had psychical seizures, and more than 252 had major convulsive seizures.

In Table 2, the scoring groups which are given in Table 1 are telescoped for convenience. The number of right and wrong predictions is shown, and with these is given

TABLE 2.—*Relation of Scoring Groups and EEG Prediction* *

Scoring groups		Below 40	40—74	75—100	100—120	Above 120	Total
Total patients		108	283	29	49	31	500
Predictions	Right	89	187	23	42	30	371
	Wrong	13	66	6	7	1	93
Slightly abnormal records		6	30	(1)	(2)	—	36+(3)
Acceptable errors below 75	Organic	9	26	(1)	(1)	—	37
	Wave-and-spike	1	14	(2)	(3)	(6)	28
	Sleep	—	4	—	—	—	4
	Family history	—	7	—	—	—	7
	Low I. Q.	—	3	—	—	—	3
Acceptable errors above 75	Sleep	—	—	2	2	—	4
	Nonconvulsive	—	—	1	2	—	3
	Psychomotor	—	—	1	—	—	1
	Provoked	—	—	1	1	—	2
Unacceptable errors		3	12	1	2	1	19

* With scores over 75 markedly abnormal records are predicted, whereas with scores under 75 normal records are predicted. The numbers enclosed in brackets are included in other figures, the "slightly abnormal records" being included in wrong predictions and the "organic" and "wave-and-spike" being included in correct predictions.

the number of EEG's classified as slightly abnormal. With scores below 75, such EEG's could have been included in correct predictions. With scores above 75 they have been included in wrong predictions, although the numbers are given in parentheses.

Wrong predictions are divided into acceptable and unacceptable errors. With scores below 75 a markedly abnormal EEG represents a wrong prediction, and with scores above 75 a normal EEG represents a wrong prediction. With scores below 75 some errors were acceptable because the patients had organic cerebral disease. With two exceptions head injuries were not made an excuse for wrong predictions, since head injury in the past has not necessarily been indicative of persistent cerebral damage. In the first exception an EEG focus was found over a bone defect, and in the second the patient had neurological signs referable to the cerebrum. We found that wave-and-spike activity, and variants of this pattern, are unpredictable except when the patient has frequent petit mal or myoclonus. Nevertheless, wave-and-spike activity was allowed as an acceptable error, since organic disease would not in any case be inferred from this EEG abnormality. Sleep seizures relative to "awake" seizures were an important source of error, for there were 8 errors for 29 patients with sleep seizures. These errors were partly explained by the difficulty in assessing the frequency of sleep seizures and partly by the fact that the number of patients was too small to permit one to work out the correct score for this seizure type. A score of 60 is probably too high. An error of prediction with sleep seizures is therefore considered to be acceptable. A family history of major convulsive seizures in near relatives, but not major nonconvulsive seizures, and a low I. Q. were made excuses for wrong predictions. Of the three patients with a low I. Q., none could read or write.

Sometimes scores over 75 were obtained even when the patient had major nonconvulsive or psychomotor seizures, owing to the combination of the frequency of the seizures and the age of onset. In three patients with major nonconvulsive seizures and in one patient with psychomotor seizures, abnormal records were, in fact, not expected, and the finding of normal EEG's was not thought to be an error of prediction. Of two other patients with scores over 75 and normal EEG's, one had frequent major convulsive seizures, always provoked by coughing, and the other had similar seizures, occurring infrequently since childhood and always provoked by unexpected pain. These two patients were thought sufficiently unusual to justify considering the errors of prediction acceptable.

When the acceptable errors of prediction are subtracted from the total errors, it is found that the number of unacceptable errors is 19, or 4% of the total.

There are 79 wrong predictions in patients with scores below 75. When the acceptable errors are subtracted, except those with organic cerebral disease, there are 50 errors. Of these 50 errors, 35 were for patients who had organic cerebral disease. In other words, if, for a patient with a score below 75, there is an unacceptable error of prediction, the patient has 7 chances in 10 of having organic cerebral disease.

Comment

There is no doubt that 500 patients is an insufficient number from which a final conclusion can be drawn with regard to the scoring system. An obvious check on the system would seem to be offered when treatment reduces the frequency of seizures, for the scores would then be materially altered. However, an inquiry along these lines proved to be disappointing. It emerged that, although energetic treatment would often reduce the total number of seizures in a specified period, it was not common for frequency to be reduced from one a week to one a month, or from one a month to one a year. The best results were obtained with psychical seizures, which often responded dramatically to treatment; and when this occurred, a reduction of the score below 75 was associated with reversion of an abnormal EEG to normal. Since a clear week with no seizures was all that was required to change the score in some patients, the return of the EEG to normal was apparent within one or two weeks after the last seizure. With major convulsive seizures the results were unsatisfactory. Patients with major convulsions more than once a week had often been subject to seizures since childhood, so that a reduction in frequency did not return their scores to normal. These patients, too, proved to be unreliable in their attendance at clinics, and of those who did attend the frequency of seizures could not be reduced sufficiently to alter the scores. It is an interesting comment on treatment that many patients will report considerable improvement although there has been no change in frequency, the improvement being in the form of a reduction of the severity of each seizure; and also that many patients will report a considerable reduction in the frequency of seizures although inquiry reveals that the periods of freedom from seizures were not increased from one week to one month, or from one month to one year.

It is striking that the interseizure EEG's associated with major nonconvulsive seizures are always normal, although undue significance should not be given to this, since such seizures tend to be infrequent. This remark is also relevant to psychomotor seizures. Only six patients in the present series had nonconvulsive seizures once a week. Three patients, however, had major nonconvulsive seizures several times a day, and despite this their records remained normal. This was never found in people with convulsive seizures. At any rate, it is clear that clinicians who wish to divide people with seizures into classes signified by epilepsy, hysteria, and syncope cannot hope for the electroencephalogram to reveal the defining properties. Indeed, even the attempt to use the EEG to distinguish between major convulsive and major nonconvulsive seizures is reduced to absurdity, for the EEG in the former is only abnormal when this kind of seizure is sufficiently frequent or long standing for an adequate description of the seizures to be obtained. In short, nothing can be inferred from the EEG which cannot be obtained from the patient and his relations. In this connection it can be stated that the abnormality rate in a series of patients can be predetermined by the selection of patients. Thus, it is possible to select patients so that the EEG's will be nearly all normal or nearly all abnormal. It is relevant at this point to mention that a prior history of major nonconvulsive seizures is not uncommon in patients complaining of major convulsive seizures. This association of nonconvulsive and convulsive seizures is perhaps not so significant as it first appears, for major nonconvulsive seizures are very common in the "normal" population and in

a hospital population are often associated with various psychomatic complaints, such as headache and peptic ulcer.

It is of some importance that roughly half of the predicted EEG abnormalities were related to psychical seizures. Accuracy in predicting an EEG therefore depends to a great extent on inducing patients to ignore, for the moment, their occasional major seizures and to discuss at some length their minor seizures. Most patients require a little prompting before they will admit seizures which, at the beginning of an interview, they say are indescribable. When they realize that these minor seizures are of interest to the physician, they generally give descriptions which leave the physician in no doubt of their vivid, obtrusive, and explosive nature. Speech seizures previously mentioned often do not come to light unless friends and relations are expressly asked about them, and this may be because the nonsensical speech is thought to be indicative of insanity. An interesting point which emerges from the study of negative and positive psychical seizures is that they occur sufficiently often to account for the appearance of all temporal lobe foci in the EEG that is, there is no evidence that temporal lobe foci are related to any other kind of seizure. The only exception is found in people with sleep seizures, which always seem to be convulsive. However, one or two patients in the present series described how they may be awakened from sleep by psychical seizures, and, consequently, it may be supposed that such seizures do occur during sleep.

Correct predictions of EEG's have only confirmatory value. An error of prediction with regard to an abnormal EEG, however, should arouse the curiosity of the physician, for, if there is no reason to doubt the accuracy of the history, there is a probability of 7 in 10 that the patient has organic cerebral disease. Perhaps this may be put with advantage in another way by saying that if an abnormal EEG is correctly predicted, it is evident from the history that the patient will require energetic medical therapy; on the other hand, if an abnormal EEG represents a wrong prediction, the patient will require careful follow-up, and possibly neuroradiological investigation. In only four patients in this series was it thought justifiable to pursue neuroradiological investigation solely on the strength of a wrong EEG prediction, and in each case organic cerebral disease was discovered—gliomas in two, carcinoma in one, and cerebral atrophy in one. This small number is due to the fact that patients with seizures and abnormal EEG's often present with neurological signs, with the result that organic cerebral disease can be inferred without reference to the EEG. These patients are generally admitted to a neurosurgical unit and do not appear in the present series. It is common in a neurosurgical unit for a patient with seizures and a cerebral tumor to have a normal score and an abnormal EEG; that is to say, wrong predictions of abnormal EEG's are common.

The method of predicting EEG's was adopted as a means of proving the scoring system. It should be apparent, however, that the scoring system is merely a method of classification in which patients are put into classes on the basis of a score above or below 75. The class, the defining property of which is a score below 75, is subdivided on the basis of EEG's, and membership of the class, the defining property of which is an abnormal EEG, allows the inference that organic cerebral disease has a probability of 7 in 10. The conclusion is that the EEG is only one of the defining properties used in the division of people with seizures for the purpose of inferring organic cerebral disease and that, since the other defining properties are brought to light in the process of taking histories, it follows that in the face of a poor history a technically perfect EEG is without value. Indeed, it may even be misleading.

Summary

A correlation is made between types of seizures, frequency, age of onset, and duration of condition, taken collectively, and EEG's.

A scoring system is described which enables this correlation to be easily made.

The correlation is sufficiently good to allow EEG's to be predicted in terms of "normal" and "markedly abnormal."

Errors of prediction are analyzed as acceptable and unacceptable. The latter amounted to only 4% of 500 patients.

It is suggested that, when an abnormal EEG represents an unacceptable error of prediction, there are 7 chances in 10 that the patient has organic cerebral disease.

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Glasgow Royal Infirmary.

Spinal Reflex Activity from the Vesical Mucosa in Paraplegic Patients

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Introduction

The reciprocal innervation of the smooth vesical detrusor and striated muscles of the pelvic floor has been well documented by cystometry, electromyography, a combination of the two, and various anesthetic procedures. Thus a good working hypothesis has been provided for physiological and pathological micturition.[1-5] According to common neurological nomenclature, therefore, only proprioceptive reflex activity has been studied. In contrast, the reflex activity which correlates stimuli of the bladder mucosa and responses of the detrusor and pelvic floor musculature has not been explored.

Three factors motivated the present study.

1. A continuing interest in the bulbocavernosus reflex,[6] which is diagnostically important in differentiating somatomotor lesions above and below the conus; this reflex becomes significant in the proper classification and treatment of patients with traumatic cord bladder because the conus contains the spinal visceromotor reflex centers of the bladder. Experience with sacral neurotomy on patients with spinal cord injury has shown that the reflex arc synapses not exclusively in S-3 (as postulated by Bing and Haymaker), but includes all sacral, and possibly the fifth lumbar, segments[7]; these findings have been complemented by investigations on normal subjects with the aid of spinal anesthesia.[8] Studies of the bulbocavernosus reflex are still in progress, and only features pertinent to the present subject will be recorded here.

2. A patient with complete physiological transection of the cord at C-6 underwent a sacral neurotomy from S-2 to S-4 in an attempt to control autonomic hyperreflexia from bladder distention. His hypertension abated promptly, but the sudomotor discharges persisted. Tetracaine U. S. P. (Pontocaine) anesthesia of the vesical mucosa was done to determine whether a possible mucosal pathway of reflex hyperhidrosis could be suppressed. This was not the case, although it was known that tetracaine anesthesia can temporarily abolish paroxysmal hypertension.[9] We believe that, in this case, the intact pathways coursing along the sympathetics sustained the hyperhidrotic reaction. Unexpected, however, was the patient's report that he voided *per urethram* for the first time in three years, despite the presence of a suprapubic cystostomy. This precipitated the thought that a reflex between vesical mucosa and pelvic floor musculature was probable, and was possibly an important component in the pathophysiology of bladder dysfunction.

3. While this experience suggested the importance of anesthetized mucosal receptors, the importance of stimulated receptors remained to be demonstrated. In the course of a study of mechanical and thermic stimulation of the bladder mucosa in normal and paraplegic subjects, it was discovered that small amounts of instilled ice water initiated the desire to void. This desire, in turn, signifies a detrusor contraction (a proprioceptive sensation), which reciprocally relaxes the pelvic floor musculature.

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Consequently, experiments were devised to study the behavior of the bulbocavernosus reflex and pelvic floor musculature, and that of the bladder, under resting conditions, under mild and intense stimulation, and under anesthesia.

Material and Methods

Patients with traumatic cord lesions of various levels and extents volunteered for the respective examinations.

As a representative of the pelvic floor musculature and a significant participant in the bulbocavernosus reflex, the external sphincter ani was chosen for electromyographic recording in all cases. For the purpose of assessing the over-all activity of the muscle, separate insulated needle electrodes were inserted approximately 1 cm. apart to form a bipolar pair. Under rectal digital guidance, positions of the needle tips within the muscle were ascertained and confirmed by recording. This method was preferred to the coaxial bipolar technique, because it excluded activity from the surrounding muscles but at the same time was not limited to pick-up from a small group of muscle fibers. It allowed a statistical impression of the activity of the entire muscle fiber population. Recording was performed on one channel of an Offner electroencephalograph.

For the purpose of tabulating electromyographic responses quantitatively, a simple scale was devised. The scale was based upon a combination of voltage, frequency of discharge, and number of active motor units. Although discharges of single motor units usually could be identified, the scale pertains to the voltage (amplitude) of the envelope of an "interference pattern." As used in clinical electromyography, the term "interference pattern" refers to an accumulation of muscle discharges, which is so dense that the wave form of the individual motor unit cannot be distinguished. The scale was as follows: "zero" (zero microvolts), minimum (up to 25μv), slight (up to 50μv), moderate (up to 75μv), great (up to 100μv), and maximum (over 100μv). Responses to stimuli were measured as the difference between the total resulting electromyographic activity and the antecedent resting level.

The bulbocavernosus stimulus was applied by (1) squeezing the glans penis, (2) pull on an intraurethral catheter with its 5 cc. Foley bag inflated, and (3) pull of a similar suprapubic catheter.

Vesical mucosal anesthesia was achieved by a 0.25% solution of tetracaine hydrochloride in distilled water (2 to 3 oz. [60 to 90 cc.]), which was drained 10 minutes after instillation.

Vesical mucosal stimulation was achieved by instillation of 2, sometimes 3, oz. of sterile ice water, which was preceded by a control trial with the same amount of sterile saline solution of room temperature.

Cystometry and sphincterometry were done by means of the Lewis apparatus[11] and a "simple sphincterometer."[12] A continuous drip with sterile water supplied the volume at the rate of approximately 25 cc. per minute. The technique was like that reported previously.[5]

Capacity-residual urine tests at the bedside were performed in the following manner: Tetracaine solution, 2, or 3, oz., was instilled into the emptied viscus, allowed to remain for 10 minutes, and drained before removal of the catheter. Capacity and residual urine were determined one hour thereafter. The type of incidental voiding was noted, whether by "reflex" or by "volitional strain."

The behavior of the voiding reflex under saline and ice-water stimulation was observed before and after tetracaine anesthesia at the bedside. Two ounces of each fluid was used.

Effect of Tetracaine Anesthesia of the Vesical Mucosa on the Electromyogram of the Anal Sphincter

(Figs. 1 and 2)

Twenty-nine examinations were done on 16 patients. Two patients had incomplete cervical lesions; seven, complete cervical; five, complete thoracic, and two, complete lumbar lesions.

The basal activity of the sphincter ani EMG decreased in 21 instances; it remained unaltered in 8 instances; in 1 case, it remained unaltered on the first trial, but decreased after a second instillation.

The electromyographic response to single or repetitive compressions of the glans penis was decreased or abolished in 9 (Fig. 1), unchanged in 14, increased in 2, and questionable in 1 instance.

The electromyographic response to single or repetitive pulls of the urethral Foley bag catheter was decreased or abolished in 16 (Fig. 1), remained unchanged in 7, and was doubtful in 2 instances. An incidental observation was the abolition of response to mucosal suction, which unpublished experiments have shown to be a very strong stimulus.

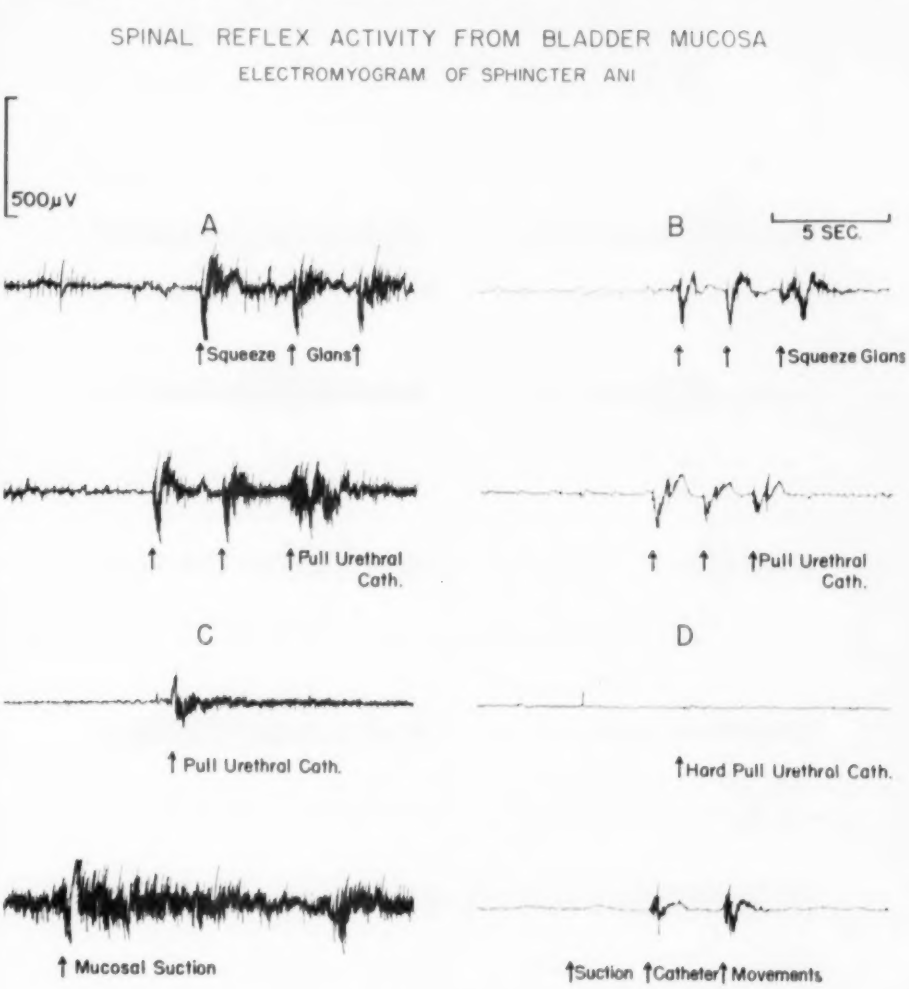


Fig. 1.—The left column of the figure represents responses to various stimuli before mucosal anesthesia with 0.25% aqueous solution of tetracaine hydrochloride; the right column, the responses to the same stimuli after anesthesia.

Patient A. Age: 46; level: C-6, complete.

A: The upper and lower tracings show anal sphincter EMG responses on testing the bulbocavernosus reflex by stimulation of the glans penis and of the bladder neck, respectively. Triple stimuli are used in each case. Note that the responses to bladder-neck stimulation (pull on a urethral catheter) summate. Not only are the second and third responses more pronounced, but the sphincter tone (as evidenced by the density of the EMG tracing) remains at a higher level after the final stimulus than is apparent before stimulation.

B: The upper and lower tracings parallel those of *A* after vesical mucosal anesthesia. The resting, prestimulus EMG activity is practically abolished, and the responses to both modes of stimulation are greatly diminished. Before stimulation, these tracings exhibit a pulse artifact (base-line deflections synchronous with the EKG), which often appears when the anal sphincter is completely relaxed.

Patient B. Age: 36; level: T-10, complete.

C and *D*: In contradistinction to *A* and *B*, which demonstrate diminution, these tracings show complete abolition of responses. The last line shows that this obtains even with one of the most potent stimuli, namely, mucosal suction. Note that catheter movements still elicit a response, via the unanesthetized urethral receptors.

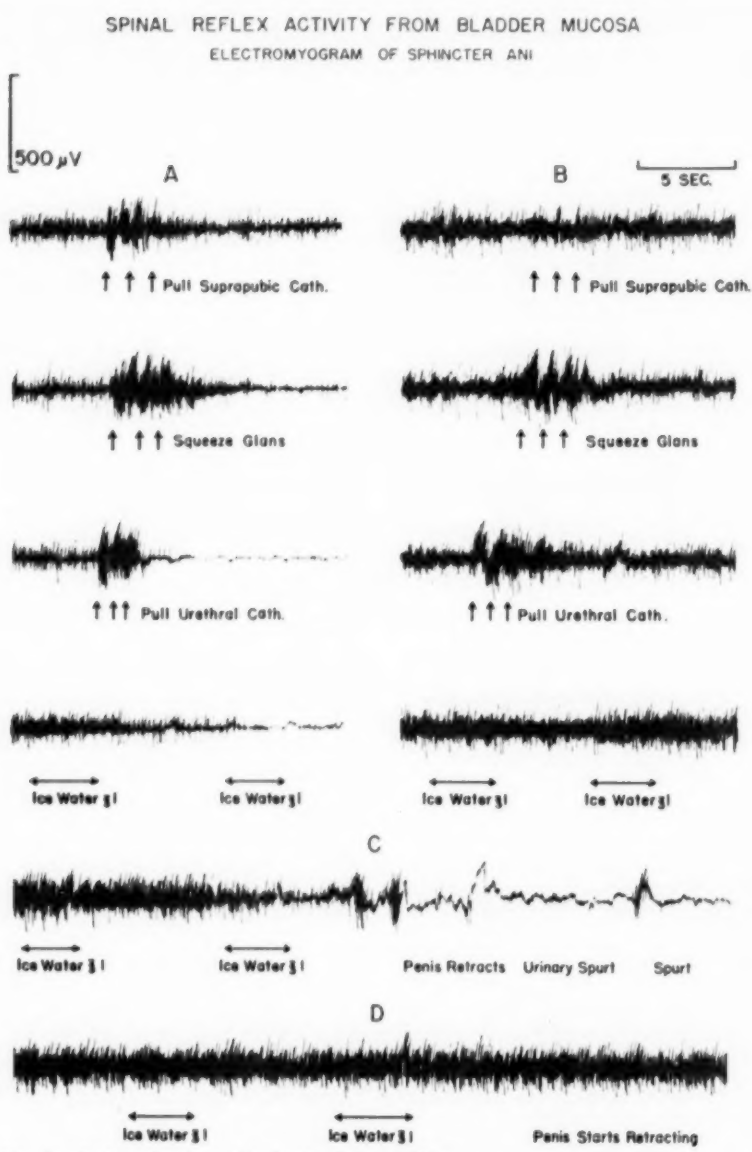


Fig. 2.—Patient C. Age: 34; level: C-6, complete.

Columns *A* and *B* show the effect of various stimuli before and after mucosal anesthesia. In each instance, inhibition of electromyographic activity follows stimulation prior to anesthesia but is abolished by anesthesia. This type of inhibition remains unexplained. In contradistinction to other cases (Figs. 1 and 4), the resting tonic EMG activity is not diminished by anesthesia. *C* demonstrates the result of ice water stimulation through a suprapubic tube after the intraurethral catheter has been removed. The response consists of an inhibition of EMG activity, associated with retraction of the penis and urinary spurts *per urethram*, i.e., a result of detrusor contraction. This response is believed to be due to either or both of two factors: (1) The mucosal anesthesia has worn off (after 19 minutes), and (2) urethral stimulation from the catheter is absent. *D*: following renewal of anesthesia, ice water stimulation under identical circumstances (as in *C*) elicits neither inhibition nor voiding but merely prodromal penile retraction.

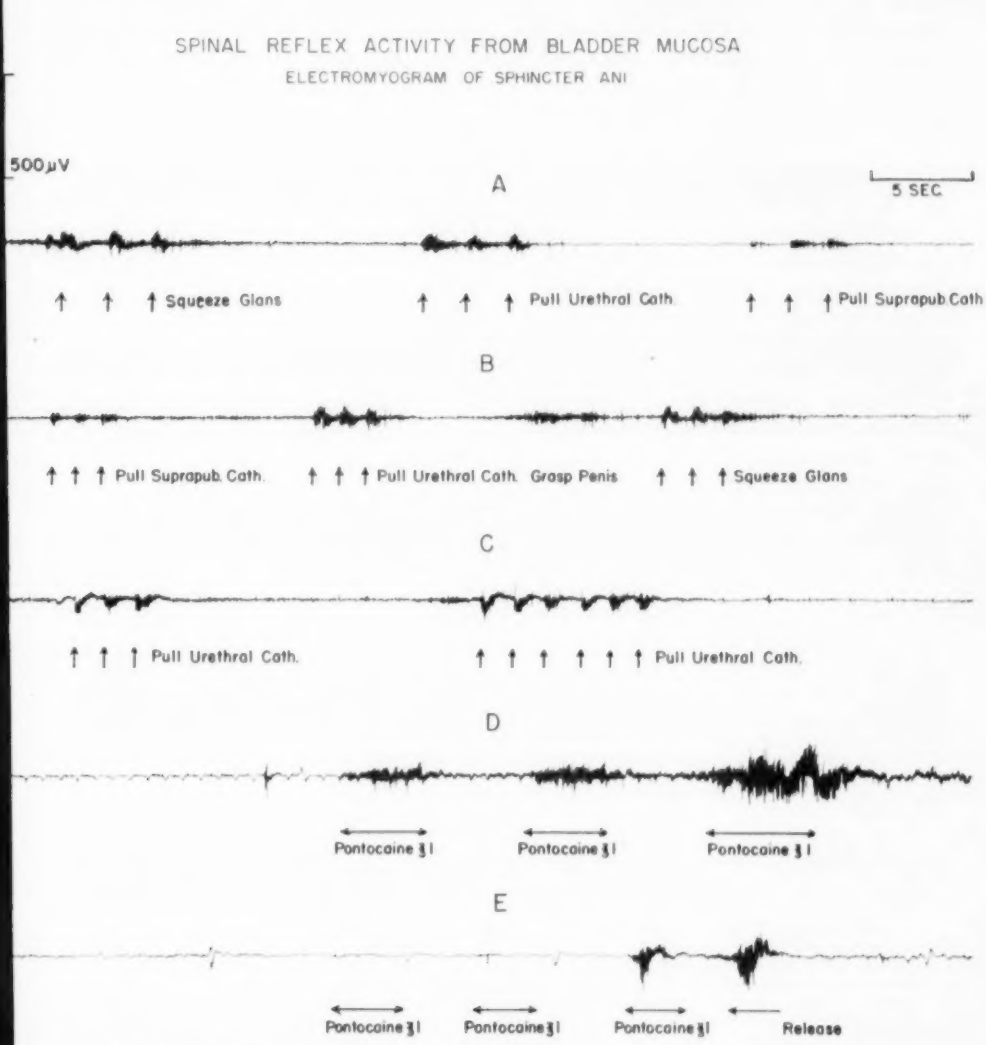


Fig. 3—Patient C. Age: 34; level: C-6, complete.

A and *B* demonstrate that the sequence of applied stimuli (squeezing glans, intraurethral and suprapubic catheter pull) does not affect their relative inhibitory potencies. *C* shows that tetracaine anesthesia increases the threshold, in that inhibition results only if the number of stimuli in short succession is increased from three to six. *D* and *E*, by the same token, show that anesthesia removes mucosal facilitatory afferents, leaving only proprioceptive afferents, and thus increases the threshold to a point where only volumetric summation results in an adequate stimulus. This interpretation is corroborated by the fact that release of the fluid (*E*) initiates an even greater response. Furthermore, comparison of *D* and *E* shows that summation in the third response of *D* is caused by both the mucosal and the proprioceptive afferents, while this summation is absent in *E*. The response to the third stimulus in *E* is considered to be exclusively myotatic.

In a few instances, inhibition, i. e., decrease of electromyographic activity, followed stimulation per glans or catheter. This inhibition was eliminated by anesthesia in four experiments with stimulation of the glans and in three with catheter pull (Fig. 2).

In a preceding, unpublished study we have noted that inhibition may be achieved as well by intermixing stimuli as by repetition of the same stimulus. In one case of the present series we confirmed our previous experience. Figure 3 shows that the sequential order of applied stimuli does not alter their relative inhibitory potencies, nor does it alter their relative excitatory potencies. Tetracaine anesthesia increases the threshold, so that inhibition results only if the number of stimuli in short succession is increased.

While summation of responses resulted rarely from repetitive compressions of the glans, it occurred frequently on catheter pulling (Fig. 1). Anesthesia abolished the summation of responses from glans stimulation in every case in which it existed. Anesthesia also abolished the summation of responses from catheter pull in the majority of cases in which it was present. An increase of summation after anesthesia seemed to occur in two cases with either stimulus. Summation apparently was unaltered in three cases with stimulation via catheter.

No correlation could be found between the level or extent of the lesion and responses observed.

Effect of Stimulation with Saline and Ice Water on the EMG of the Sphincter Before and After Mucosal Anesthesia

(Figs. 3 and 4)

Examination was made of 15 patients; 3 had incomplete lesions at C-5, C-5 and C-6, and C-6, respectively; the rest had

Fig. 4.—Patient B. Age: 36; level: T-10, complete.

Top left: The anal sphincter EMG shows a sustained response to insertion of needle electrodes—not "insertion potentials" in the usual sense of mechanical excitation of muscle fibers impinged upon, but an "interference pattern" of tonic motor unit activity resulting reflexly from (1) myotatic stimulus of a foreign body within the muscle, and/or (2) the "pain" stimulus of penetration of the skin, the sphincter participating in a "mass reflex" involving the entire spastic muculature of the pelvic floor.

Top center: Adaptation to the stimuli of electrode insertion eventuates in almost total relaxation.

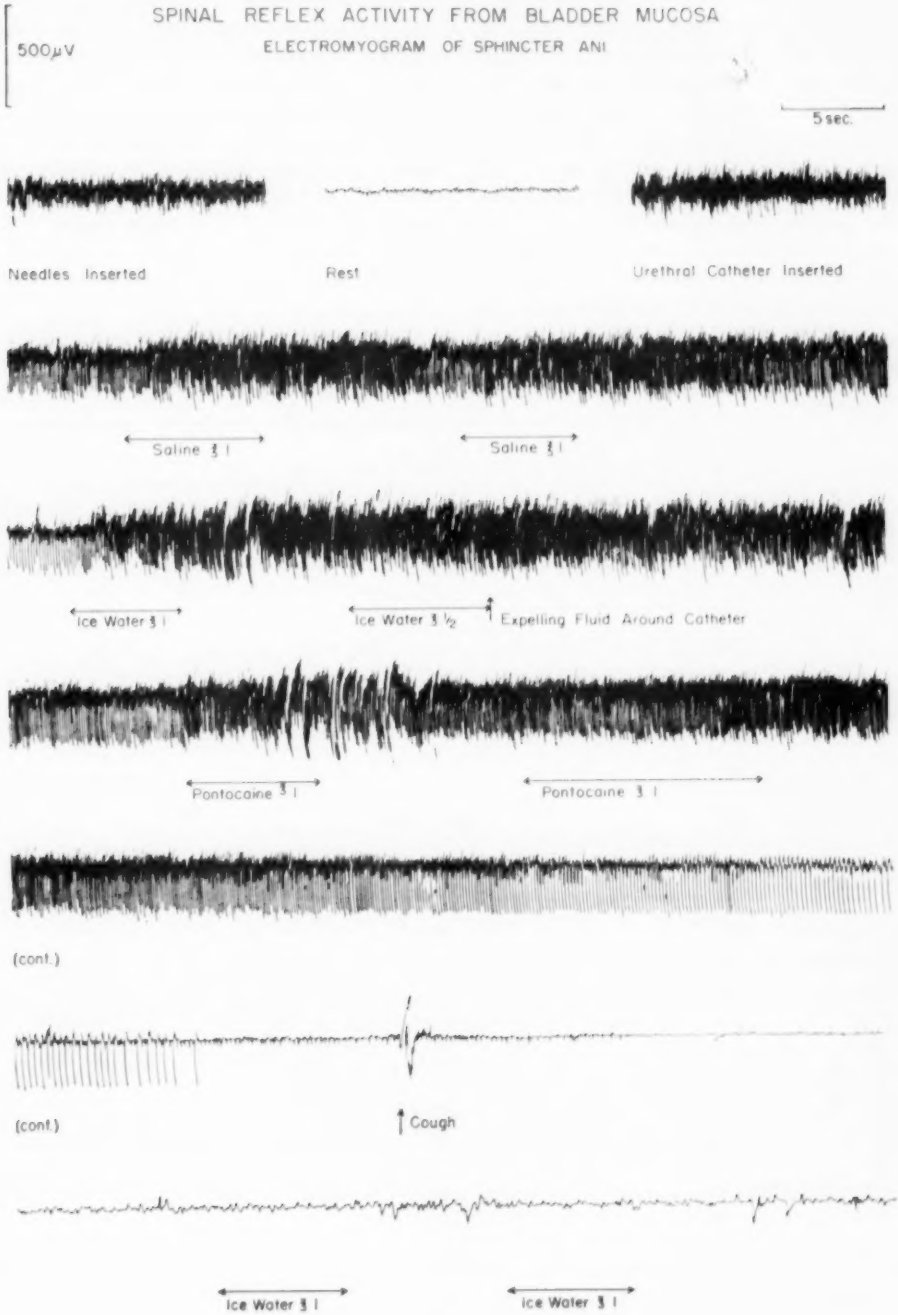
Top right: Urethral catheter insertion supplies stimulation through a different afferent pathway, one which, in this patient, is not subject to adaptation. The sphincter ani again shows an "interference pattern" of tonic contraction, but the contraction persists indefinitely.

Second strip: On a background of tonic EMG activity, the responses to two instillations of isotonic saline can be discerned as a "thickening" of the interference pattern of the numerous motor unit discharges. Two separate increases in density of the tracing appear, each lasting about 10 seconds.

Third strip: At the very beginning of the strip, tonic EMG activity is relatively slight; the high amplitude of the recording is due to a single, rhythmically firing motor unit, with which one of the electrodes happened to be in close contact. Instillation of 1 oz. (30 cc.) of ice water elicits an explosive EMG response, and no recovery is evident before the second ounce is instilled. The responses summate and result in a protracted increase of EMG activity. The second instillation is terminated by a strong detrusor contraction, which forces the fluid out around the catheter. About five seconds after the onset of this contraction, the sphincter activity decreases slightly.

Fourth, fifth, and sixth strips: These strips comprise a continuous recording of the sphincter EMG response to vesical mucosal anesthesia with 0.25% aqueous solution of tetracaine hydrochloride. At the beginning, the tonic background activity is moderate, and the high amplitude (250μv) of the tracing is again due to the single motor unit which dominates the previous strips. Recording of this motor unit is opportune because it reflects, as a representative member, the processes of relaxation which affect the entire motor unit population of the sphincter. Just as this one unit slows its firing frequency from 10 to 1 per second and then quits, so does the background (solid black) activity diminish in density and finally expire, despite the presence of the urethral catheter.

Seventh strip: Under vesical mucosal anesthesia, the anal sphincter is completely relaxed. The small ripples in the base line are probably due to movement and to EMG potentials from distant muscles. Repetition of the two ice water stimuli is utterly ineffectual in reviving sphincter activity. This illustrates the importance of vesical mucosal receptors as a source of facilitatory afferent impulses for the maintenance of anal sphincter tone and as moderators of the bulbocavernosus reflex.


SPINAL REFLEX ACTIVITY FROM BLADDER MUCOSA
ELECTROMYOGRAM OF SPHINCTER ANI
500μV
5 sec.
Needles Inserted
Rest
Urethral Catheter Inserted
Saline ½ l
Saline ½ l
Ice Water ½ l
Ice Water ½ l
Expelling Fluid Around Catheter
Pontocaine ½ l
Pontocaine ½ l
(cont.)
(cont.)
Cough
Ice Water ½ l
Ice Water ½ l

clinically complete lesions, 1 of which was C-4, 1 at C-5, 4 at C-6, 1 at T-4, 2 at T-6, 1 at T-10, and 2 at L-1. One of the last lesions was "mixed," in that it was an upper motor neuron lesion somatically but a lower motor neuron lesion autonomically, as demonstrated cystometrically and by the inability of the detrusor to eject 1-2 oz. (30-60 cc.) of instilled sterile ice water. Thus, all patients had somatically upper motor neuron lesions. Only one of the patients, with a lesion at C-6, had a suprapubic catheter; the rest had intraurethral Foley bag catheters.

All 15 patients responded electromyographically to saline or ice water instillation before mucosal vesical anesthesia with tetracaine. After anesthesia, these responses were altered in all but one case; this was the patient with a "mixed" lesion at L-1.

In 13 cases the alteration consisted of either a decrease or a complete abolition of the basal activity at rest and of the electromyographic response to the stimulus (Fig. 4).

That fluid instillation constitutes a mucosal stimulus in the quantities used is demonstrated in Figure 3 (lines *D* and *E*).

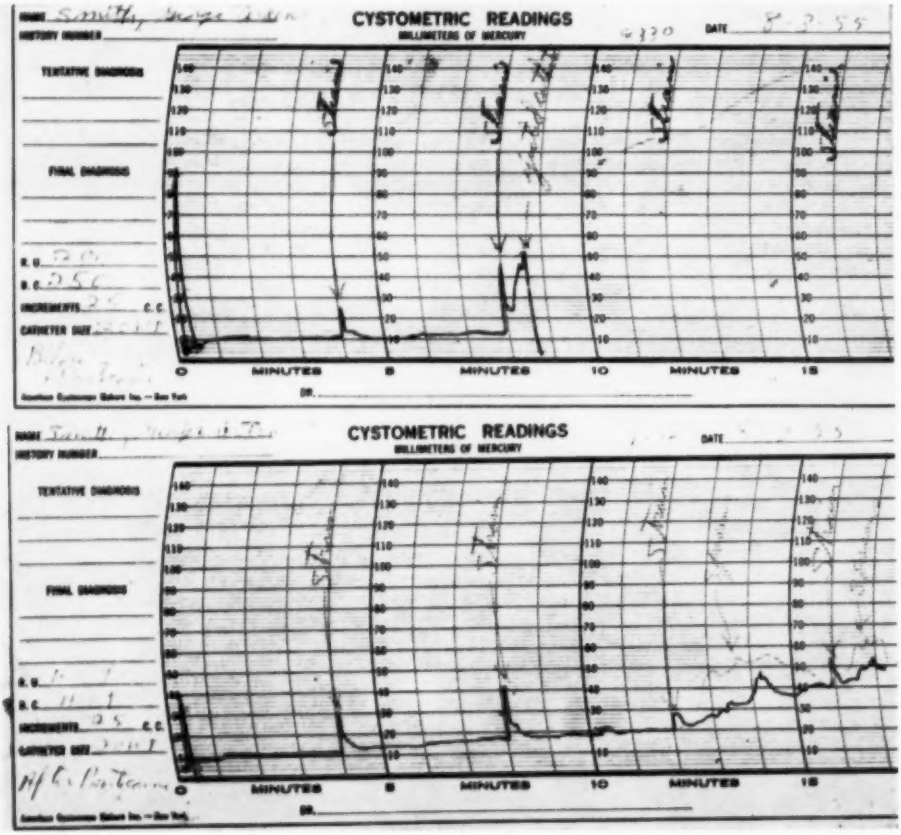


Fig. 5.—Patient B. Age, 36; level: T-10, complete.

The upper and lower tracings are sphincterometric and cystometric recordings obtained before and after mucosal anesthesia. Note that sphincterometric values diminish from 90 to 40 mm. Hg, the capacity increases from 250 to more than 400 cc., the peaks caused by volitional abdominal pressure mark 100 cc. increments (every four minutes); the tone (slope of the curve) increases, in this particular patient. The recording was terminated by ejection of the catheter before, but not after, anesthesia.

In this case, removal of mucosal afferents by topical anesthesia increased the threshold to the point where only volumetric summation resulted in an adequate (myotatic) stimulus.

In one case (C-6 complete lesion), the response consisted of inhibition rather than activation of the electromyogram before anesthesia (Fig. 2, lines 4-6). This inhibition was accompanied by voiding in one instance (Fig. 2C). Following anesthesia the inhibition was abolished.

Effect of Mucosal Anesthesia on the Cystometrogram

(Fig. 5)

A total of 19 patients were examined; 9 patients had complete cervical, 6 complete thoracic, 1 a complete lumbar, and 3 incomplete cervical lesions. Capacity and residual urine, tone, autonomous waves, uninhibited contractions, micturition reflex, sphincterometric data, and balance of bladder function (expressed by ratio residual/capacity) were evaluated. These functions were tabulated in terms of increase, decrease, or lack of change. The majority showed a marked increase of capacity and residual urine (13 and 12 patients, respectively); the tone tended to decrease (9 patients); and contractions, both autonomous and uninhibited, remained unaffected in more than one-half the patients; sphincterometric reading showed a decremental trend (8 patients); the balance of bladder function improved in 8 and remained unaltered in 9 patients. It should be noted, however, that the improvement was neither permanent nor optimal. Figure 5 shows increase of capacity and tone, decrease of sphincterometric values, and unchanged balance.

Effect of Mucosal Anesthesia on Bladder Function *

A total of 49 patients were subjected to 122 examinations. Of the 49 patients, 35 had complete lesions (18 cervical, 15 thoracic, 2 lumbar) and underwent 79 examinations; 14 patients had incomplete lesions (9 cervical, 4 thoracic, 1 lumbar) and underwent 43 examinations.

Of 122 trials, the capacity urine increased in 57.5%, decreased in 40%, and remained unchanged in 2.5%. The residual urine increased in 39%, decreased in 52%, and remained unchanged in 9%.

"Functional improvement" does not refer to "balanced bladder function," as defined elsewhere[24]; the term refers to (1) cases in which the bladder expelled urine after anesthesia, but not prior to anesthesia, and (2) cases in which the residual-capacity ratio improved postanesthetically. Functional improvement occurred in 51%, and no improvement, in 49%.

Although changes in capacity and residual urine were independent of the extent of the lesion, there appeared to be a relationship to the level; capacity urine increased and residual urine decreased, with a notably greater frequency in trials on patients with thoracic lesions than in all others.

No consistent relationship was noted between functional improvement and the direction of change of capacity and residual amounts.

An interesting incidental observation was the fact that five patients responded to mucosal anesthesia with marked improvement of bladder function, while pudendal nerve anesthesia had been ineffective. Four patients had cervical, and one a lumbar, lesion.

Equally of interest was the observation that six patients, two of whom were not among the above series, benefited permanently from mucosal anesthesia. Two patients had only one instillation; the rest had repeated anesthesias.

It is thought worth while to report on these six patients in more detail. One patient with multiple sclerosis and a cervical neurological deficit, whose bladder function had regressed following a pyelonephritic bout, responded well to repeated instillations. Another patient had a traumatic lumbar

* Dr. George K. Kawaichi assisted with these studies.

upper motor neuron lesion; his bladder had not regained reflex function in 11 months but did so after a series of anesthesias. A third patient had a lumbar mixed lesion; although he had a flaccid paralysis of the lower extremities and the detrusor muscle, he had an upper motor neuron lesion of the pelvic floor musculature, as demonstrated by a bulbocavernosus reflex. His bladder emptied by strain, following a series of anesthesias. A fourth patient had a traumatic incomplete cervical lesion, but his bladder had not resumed satisfactory function in 29 months; it did so after a series of tetracaine instillations. A fifth patient had a traumatic sacral incomplete upper motor neuron lesion, which did not prevent him from walking but interfered with his bladder function; following a pudendal nerve anesthesia, the bladder function was good for three months and thereafter regressed spontaneously, without known cause; one instillation of tetracaine restored the function.† The sixth patient had a congenital partial aplasia of the sacrum, a flaccid bladder, but spastic pelvic floor musculature; although he did not respond to pudendal blocks, he gained satisfactory bladder function after one tetracaine trial.

Suppression of the Detrusor Response to Ice Water Stimulation, by Vesical Mucosal Anesthesia

The instillation of ice water (1–2 oz.) was found to be a strong stimulus in patients with upper motor neuron lesions. In addition to the 22 patients described below, 45 patients with upper motor neuron lesions consistently have shown the same detrusor response to the stimulus of ice water. The ice water was instilled through a No. 20 whistle tip catheter, which was immediately removed. It was preceded, for comparison, by a trial of the same amount of saline. After anesthesia with tetracaine, ice water stimulation was repeated. In every case, whether the testing fluid was spontaneously expelled or not, a test of residual urine by catheterization preceded the next trial.

† This patient was seen through the courtesy of Dr. C. M. Stewart, Los Angeles.

The effect of ice water (and saline) stimulation was tested in a group of 22 patients; 12 of these had upper motor neuron lesions (6 complete and 2 incomplete cervical, 4 complete thoracic). Two patients had "mixed" lesions at L-1 (autonomically lower, and somatically upper, motor neuron lesions). Eight patients had lower motor neuron lesions; six had thoracic levels, and two had lumbar levels.

Ice water stimulation was followed by detrusor contraction, with ejection of the instilled fluid immediately or within a few seconds. In some cases it was impossible to instill the second ounce of ice water because of the powerful detrusor contraction, which expelled the catheter with the contents of the bladder. None of the cases with a "mixed" or with a lower motor neuron lesion (i.e. 10 patients) expelled ice water. Only in two cases was saline partly expelled prior to the ice water. One of these had a cervical, the other a thoracic, upper motor neuron lesion.

In the 12 patients with upper motor neuron lesions, mucosal anesthesia abolished the effect of ice water stimulation in 8, but not in 4, even if urethral mucosal anesthesia was added. Two of these four did not tolerate the instillation of tetracaine, and one ejected even the catheter. However, when one of the four was tested again with ice water stimulation during spinal anesthesia, the ice water effect was promptly abolished. In rare instances, an erection following anesthesia temporarily interfered with the ejection of ice water. It is noteworthy that in all four patients whose detrusor response to ice water was not inhibited by tetracaine, EMG activity of the sphincter ani was either diminished or abolished. In confirmation of previous experience during cystometry, contraction of the tunica dartos and retraction of the penis signalized micturition in some cases.

Comment

The bladder, like any hollow viscus, is endowed with visceresthesia. Receptors are contained in the mucosa and muscularis. For

the sake of simplicity, and in line with general neurological nomenclature, we propose that responses resulting from mucosal stimulation be termed "exteroceptive," and those from muscular stimulation, "proprioceptive." [10]

An exteroceptive viscerosomatic or viscerovisceral reflex pattern has not been described for the bladder. To our knowledge, the only reports of exteroceptive viscerosomatic reflexes refer to the stomach,[13] and those of an exteroceptive viscerovisceral reflex pertain to the gastrointestinal tract.[14]

Yet it is well know by clinicians that inflammation of the vesical mucosa can, depending on its intensity, lead to frequency and stranguria. Frequency represents a facilitation of the detrusor muscle alone, while stranguria is caused by extension of facilitation to the striated pelvic floor musculature.

In order to avoid introducing a new and unfamiliar term, we have deliberately retained the name "bulbocavernosus reflex" in referring to responses of the striated pelvic musculature, as represented by the anal sphincter. We are fully aware that these responses can be elicited by a multitude of stimuli, to the vesical or urethral mucosa, to the penile skin, to the corpora cavernosa and corpus spongiosum, and to the stretch receptors of the detrusor muscle.

In the majority of cases, the resting EMG activity of the anal sphincter was abolished, or at least considerably diminished, by mucosal anesthesia. The responses to stimulation of the glans penis were similarly decreased or abolished, but numerically less so than those resulting from pull on the Foley bag. The logical conclusion seems to be that there is facilitation which emanates from mucosal receptors to pelvic floor musculature. The degree of this facilitation varies from patient to patient. That silencing of mucosal receptors by anesthesia results in decrease or abolition of responses to Foley bag stimulation in a majority of instances is not surprising, since this stimulus is mediated largely through the same receptors. Furthermore, it appears that the very strong stimulus of mucosal suction is entirely confined to these receptors in some cases. What is surprising is the fact that even a remote stimulus, i. e., glans compression, should be rendered impotent, although in a smaller number of cases. This all seems to imply, then, that mucosal receptors are essential for tonicity of the striated muscles of the pelvic floor in most cases.

The mechanism of inhibition of EMG activity of the anal sphincter is only partly understood. 1. One can explain inhibition when it is associated with reflex voiding, which also has been observed by others.[1-3] This is based simply upon the known reciprocal relationship between detrusor and pelvic floor. Anesthesia removes the mucosal facilitation (by ice water) of the detrusor, and neither voiding nor inhibition results. 2. Unexplained remains the inhibition of the pelvic floor which is not associated with reflex voiding and still diminishes with mucosal anesthesia. Perhaps this could be considered as a negative feed-back, such as modifies spinal reflexes in general. However, these experiments would have to be repeated with synchronous intravesical pressure recordings; it is conceivable that this inhibition is also associated with a detrusor contraction, only of insufficient magnitude to result in actual reflex voiding.

The preponderance of summation of responses from stimuli of catheter pull over that of compression of the glans is in line with the summation which results from instillation of saline, tetracaine, or ice water; all these summating stimuli are essentially mucosal in type, while those of the glans are not. Summation indicates the importance of mucosal receptors as sources of impulses which the spinal cord recruits into a facilitatory outflow for the maintenance of pelvic floor muscle tone. Such a role of the mucosal receptors is corroborated by the depressing effect of mucosal anesthesia on the phenomenon of summation. Why an increase of summation followed anesthesia

in two cases, and why summation remained unaltered in three cases, is conjectural.

While varieties of mucosal stimuli (saline, tetracaine, ice water) differ in their potencies for eliciting a voiding spinal reflex contraction of the detrusor, their potencies are almost uniform in activating reflex contractions of the sphincter ani. This implies that the two different reflex arcs, namely, mucosa-sphincter ani and mucosa-detrusor, operate at different thresholds; i. e., the threshold of the sphincter arc is lower than that of the detrusor arc.

While, of the two exteroceptive reflexes, the mucosa-sphincter arc is the more sensitive, it is also found to be more sensitive than the proprioceptive destrusor-sphincter ani reflex arc. Perhaps myotatic detrusor receptors are stimulated subliminally by even small amounts of instilled fluid, but the true threshold of this reflex becomes demonstrable only after the overwhelming torrent of mucosal impulses has been eliminated by anesthesia. However, it should be emphasized that the relative thresholds of the mucosa-sphincter and detrusor-sphincter arcs are dependent upon the pathophysiological condition of the entire viscus.

Cystometry, done in 19 patients, confirmed graphically the 122 bedside observations, which have been reported under the heading "Effect of Mucosal Anesthesia on Bladder Function." The increase of capacity in a majority under topical anesthesia is interpreted as the effect of removal of activating impulses from the mucosa to the detrusor. An analogous dampening effect of topical anesthesia on the mucosa-sphincter ani reflex arc has just been discussed. These effects of tetracaine on both the mucosa-detrusor and the mucosa-sphincter arc may explain the paradox of a newly acquired ability to urinate despite an increased capacity and a frequently decreased tone. Owing to the relaxed pelvic floor, voiding becomes possible, usually by abdominal strain and Credé pressure, but occasionally also by detrusor reflex; the latter is presumably due to the persistence of uninhibited waves, which, being of spinal origin, demonstrate that the reflex arcs are merely dampened and not abolished. Unexplained remains the other paradox of decreased bladder capacity (in some cases) after mucosal anesthesia; a similar condition was seen following pudendal nerve anesthesia,[5] which interrupts the proprioceptive feed-back of an overfacilitated pelvic floor with its inhibitory effect on the detrusor.

Bedside observations showed that improvement of bladder function occurs—at least temporarily—in half the patients. Permanent improvement, which permitted the removal of a catheter, was seen in six patients. In adding 15 patients, not reported in this series, 21 (18%) of a total of 115 patients established satisfactory bladder function, or recovered it when it was lost by regression, not uncommon in traumatic paraplegia. That the age of the cord lesion is not prohibitive to establishment of permanent function was demonstrated by a patient who became catheter-free by mucosal anesthesia 29 months after injury; this parallels experiences with pudendal anesthesia—yet two different reflex arcs are involved in these two procedures, as corroborated by the following observations. In this series mucosal anesthesia has been effective in five cases in which pudendal nerve anesthesia failed. In another study, now in progress, the reverse was found. Furthermore, there were still other cases which responded equally well to either of the two procedures. Thus it would appear as though delicate balance were present among the various conflicting pathways. In one group of cases, exteroceptive impulses; in a second group, proprioceptive impulses, and in a third group, both extero- and proprioceptive impulses are responsible for the shifting of the fulcrum of the spinal balance. One cannot predict a priori to which category the respective case will belong until the anesthetic procedures have been attempted.

Stimulation of mucosal afferents has been known to elicit pathological autonomic

reflexes, part and parcel of which is paroxysmal hypertension, in patients with high thoracic or cervical cord lesions. It has been reported, furthermore, that tetracaine anesthesia can partly quell these reflexes.[9]

It is not surprising that ice water produces strong responses. The fact that it is ineffective in patients with a lower motor neuron type of bladder makes it a differential diagnostic tool; in this connection, it is of interest that two patients, not included in this series, failed to respond to ice water stimulation until the post-traumatic spinal shock had abated. Voiding after ice water stimulation can be explained in the following manner: Ice water activates the two exteroceptive arcs to detrusor and sphincter; the resulting contractions of these two muscles are reciprocally inhibitory through proprioception; yet the fact that voiding occurs with an upper motor neuron type of bladder means that the detrusor effect is the more potent. To what extent a proprioceptive positive feed-back (detrusor-detrusor) contributes to this potency remains conjectural.

Mucosal receptors are unable to distinguish among the modalities of touch, pain, thermic, and chemical stimulation; of these, touch and pain are nocent; the other two are perceived vaguely as referred segmental sensations via vasomotor reflexes, or as the desire to void caused by detrusor contraction. Where saline and tetracaine were ejected rarely, ice water was expelled in all cases with upper motor neuron lesions. This effect could be suppressed by topical anesthesia in 8 of the 12 examinations. In the four remaining patients, the failure of (even additional urethral) anesthesia must not be attributed to a direct chilling effect on the detrusor muscle; rather, one must assume a lowered myotatic reflex threshold, manifested by the fact that saline, tetracaine, and even the catheter, were ejected by a hyperactive detrusor. That the ice water effect is a spinal reflex, and not a peripheral, intramural one, was confirmed by the efficacy of spinal anesthesia in one of these four cases.

When topical mucosal anesthesia is used in a hollow viscus, having absorptive properties, one may be tempted to attribute its effect to (1) penetration into the submucosa and action on the submucosal nerve plexus and ganglion cells, and (2) to intravenous absorption.

A solution of 0.25% tetracaine hydrochloride, as used in our experiments, is hypotonic (isotonic is a 5% solution). The chloride content of the molecule is negligible, in regard to reabsorption as an electrolyte solution.[15] Therefore, the reabsorption rate of our tetracaine solution can be compared with that of distilled or plain water,[15] which is slow, namely, 0.04 cc. per minute,[16, 17] or 0.4 cc. per 10 minutes, i. e., the time of exposure of the mucosa to the anesthetic agent. Although "in rare instances ganglion cells . . . singly, in pairs and in small clusters," were found by Swenson et al.[18] in the superficial muscularis and submucosa, it appears at least unlikely, although theoretically conceivable, that an amount of 0.4 cc. of 0.25% tetracaine solution (containing 1 mg.), distributed over the entire submucosa of the bladder, would suffice to alter the function of the nerve elements of the submucosa. On the other hand, sensory nerve fibers are reported to penetrate into the epithelium, "between the cells of which they form free end branchings,"[19] which can readily come in contact with the anesthetic agent.

By the same token, the amount of 1 mg. of tetracaine hydrochloride would probably not act, by the intravenous route, on the detrusor and striated pelvic musculature. The bottom four tracings of Figure 4 would of themselves suffice to refute any absorptive theory of tetracaine action, because the effect was complete within 15.6 seconds following the instillation; if the reabsorption of water is 0.04 cc. per minute, then only 0.01 cc. of volume could have been absorbed in one-quarter minute, namely, 25γ of tetracaine. If still further refutation were needed, it is supplied by four cases in which tetracaine did not suppress detrusor contraction,

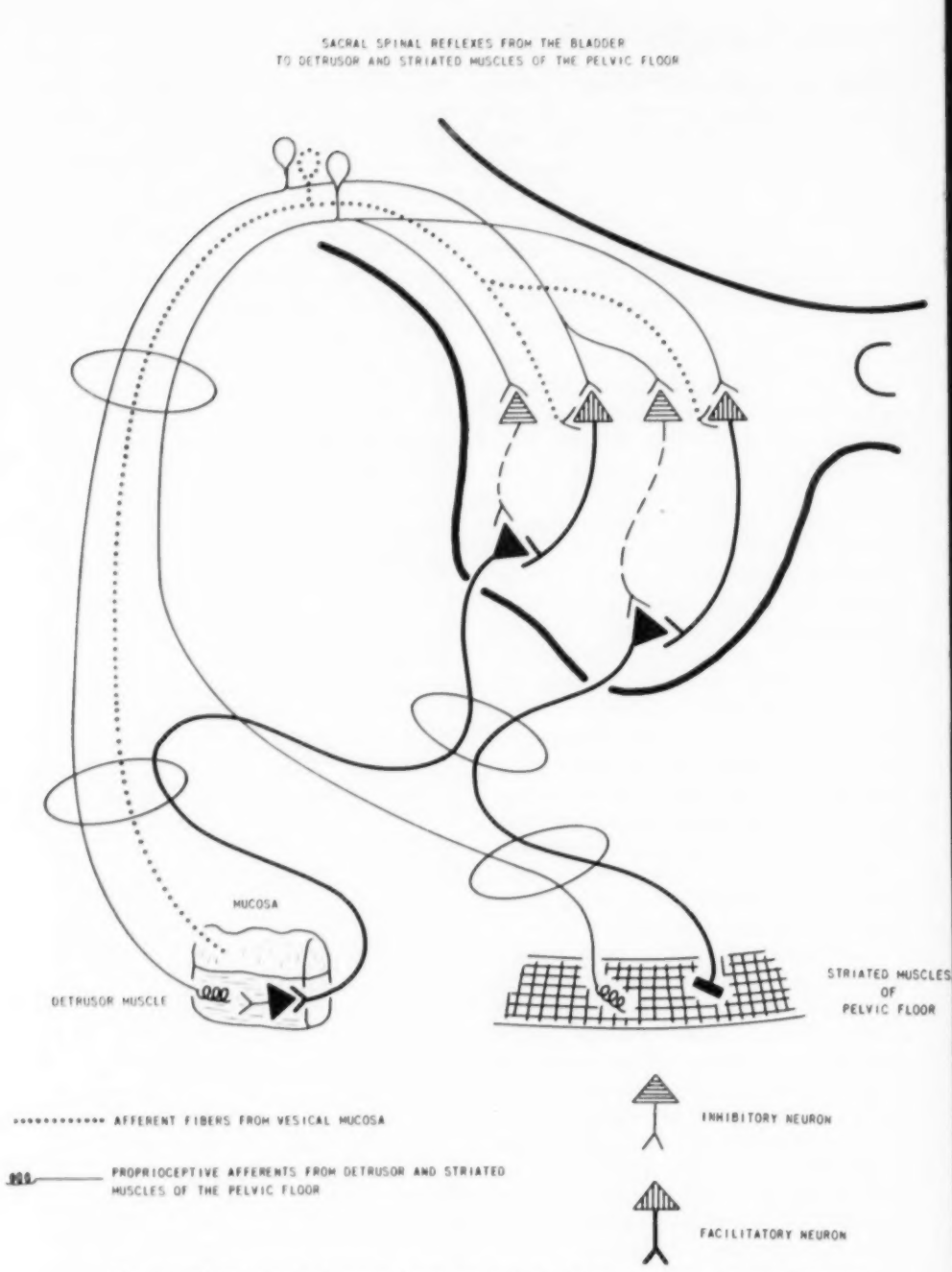


Fig. 6.—This schematic diagram shows one-half of the gray matter of a sacral segment, with its afferent and efferent connections to the striated muscles of the pelvic floor, to the smooth bladder muscle, and to its mucosal lining. The circles embrace fibers coursing in the posterior root (left upper), anterior root (right upper), pelvic nerve (left lower), and pudendal nerve (right lower). The simplified nerve network shown in the diagram is based upon a combination of concepts, one of which is the currently accepted reciprocal, proprioceptive reflex pattern; and the other, the mucosal reflex pattern postulated on the basis of the present study. Afferent and efferent pathways contained in the sympathetics are not shown in the diagram.

yet diminished or eliminated EMG activity of the anal sphincter. By the same token, there were two cases in which the reverse was true, namely, a nullification of detrusor activity without any effect on the sphincter EMG.

In conclusion, our findings are condensed as a working hypothesis, subject to changes if new facts should be contributed, in the diagram of Figure 6. Some phenomena are better understood by directing attention to the center of the diagram and thence peripherally. Thus it is obvious[5] that complete abolition of all incoming and outgoing impulses, by means of spinal anesthesia, subarachnoid alcohol block,[20] sacral neurotomy, or sacral anterior and posterior rhizotomy,[21] may improve cord bladder function by eliminating the autocracy of the delicate balance in the sacral reflex centers. Also, the effect of differential sacral neutrotomy can be better explained as a reduction of mucosal afferent activating impulses which course along mixed nerves (pelvic nerves) and, therefore, cannot be interrupted individually by surgical means. The additional reduction of motor pathways to detrusor and pelvic floor by this procedure weakens proprioceptive positive feed-back as well.

If posterior rhizotomies are done at all levels below a cervical cord transection (Scheibert's monkey experiments[22]), deafferentiation has an effect on the viscus similar to that observed by Lassek[23] on the extremity of monkeys. Motor paralysis results on a reflex basis. However, if only the posterior roots below T-10 are severed,[9] this result fails to materialize. This is understandable, because the splanchnic supply (mucosal afferent and smooth sphincter efferent) is not completely destroyed. The implied significance of the splanchnics is not shown in the diagram because it deserves further investigation.

Motor paralysis of detrusor and pelvic floor by anterior rhizotomy is self-explanatory.

Section of the pelvic nerves not only causes motor paralysis of the detrusor but interrupts also the proprioceptive and, equally important, the exteroceptive reflex arcs.

Obviously, interruption of the pudendal nerves has nothing to do with the mucosal reflex activity of the bladder.

Based upon the above considerations, a study is now in progress to evaluate the merits of tetracaine anesthesia as a therapeutic tool in comparison with pudendal and differential sacral nerve anesthesia. Provided that no obstructive uropathy exists, these three methods are tried, in the order mentioned, before surgical interventions are considered, be they nerve interruption or transurethral resection of the vesical neck.

Summary

Evidence is presented which demonstrates the importance of the bladder mucosa as a receptor influencing various spinal reflex arcs in paraplegic patients.

Of these reflex arcs, the mucosa is directly involved in two: mucosa-detrusor and mucosa-pelvic floor musculature; by feed-back mechanisms, it is believed to be involved indirectly in the following arcs: detrusor-pelvic floor, pelvic floor-detrusor, detrusor-detrusor, pelvic floor-pelvic floor. While we call the indirectly influenced arcs proprioceptive, we call the directly activated arcs exteroceptive.

The exteroceptive arcs have a modulating effect not only upon the proprioceptive arcs but also upon themselves.

This modulation first became apparent when changes in the bulbocavernosus reflex were achieved by stimulation or anesthesia of mucosal afferents. The term "bulbocavernosus reflex," as used here, embraces all responses of the pelvic floor musculature which may be elicited by stimulation via the glans penis, the urethral and bladder mucosa, and the detrusor. The influence of mucosal afferents on the detrusor was shown by stimulation before and after topical tetracaine (Pontocaine) application.

The threshold of the mucosa-sphincter ani reflex arc was lower than either that of the mucosa-detrusor arc or that of the proprio-

ceptive detrusor-sphincter ani arc in regard to three stimuli (saline, tetracaine, ice water instillation).

Ice water was found to be the most potent mucosal stimulus, but one effective exclusively in patients with upper motor neuron lesions. It was ineffective in patients with lower motor neuron lesions and during spinal anesthesia or spinal shock. It is thus of differential diagnostic value.

Temporary improvement of bladder function followed tetracaine anesthesia in one-half of the cases studied; permanent improvement resulted in a small number.

The techniques used in this study consisted of electromyography of the anal sphincter, sphincterometry and cystometry of the bladder, and bedside measurements of bladder capacity and residual urine.

The results obtained from these various techniques are discussed, and a diagram is presented which illustrates our present concept of spinal bladder reflexes in paraplegic patients.

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Vasocardiac Effects of the Circle of Willis

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Under a combination of critical and evidently fortuitous conditions of relatively light anesthesia, low body temperature, and local vascular pathology, surgical manipulation of an intracranial aneurysm or adjacent segments of the circle of Willis [1] (Fig. 1) in five successive cases repeatedly resulted in serious, although transitory, alterations in cardiac rate or rhythm.

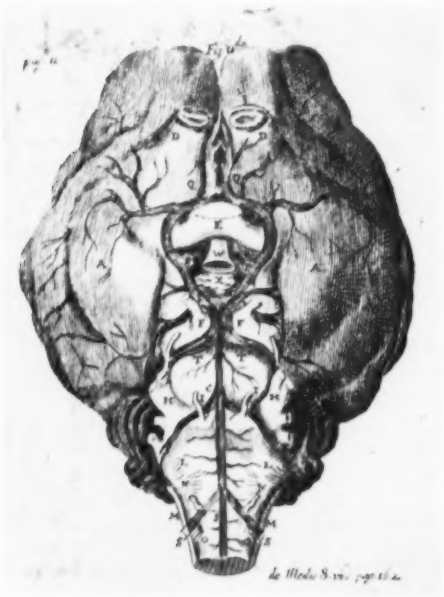

Fig. 1.—The circle of Willis, as delineated in the 1676 edition of "Opera omnia," [1] published by S. de Tournes, Geneva.

While brief runs of bradycardia or tachycardia and cardiac arrhythmias occasionally occurred in these five patients spontaneously, more frequently they resulted from certain maneuvers, such as shifting the position of the head, dissecting the carotid bifurcation in the neck, or opening the dura and, most consistently, from manipulation of the aneurysmal sac or adjacent segments of the circle of Willis during their exposure.

Since these five cases were the first in which my colleagues and I used hypothermia, a relatively light plane of anesthesia was purposely maintained because at that time a deeper plane of anesthesia in conjunction with hypothermia was considered hazardous. In two of these five cases, however, additional thiopental (Pentothal) sodium was given, which prevented further EKG changes from any form of stimulus. In five patients subsequently operated upon for intracranial aneurysm under similar conditions of hypothermia, but with a deeper plane of thiopental sodium anesthesia throughout, no EKG changes occurred at any time during craniotomy or exposure of the circle of Willis (Table 1).

Cardiac arrhythmias were characterized on some occasions by the onset of bradycardia at a rate of 20 to 60 per minute accompanied by frequent extrasystoles, or by lower nodal tachycardia at a rate of 100 to 130 per minute with accentuation of the T wave, depression of the S-T segment, and absence of the P wave, suggesting a nodal rhythm. While a drop in blood pressure sometimes coincided with such cardiac arrhythmias in three of these five cases, in two others there was no associated alteration of the blood pressure.

Without hypothermia minimal but definite cardiac effects were induced by manipulation of segments of the circle of Willis in only 3 of 11 additional patients so tested, 10 having been operated upon under general, and 1 with local, anesthesia. Of these

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From the Service of Neurological Surgery, Neurological Institute, Presbyterian Hospital.

TABLE 1.—*Alterations of Cardiac Rate or Rhythm During Intracranial Surgery*

	No. of Cases Tested	Spontaneous	On Procedural Maneuvers*	On Dissecting Cortical Vessels	On Dissecting Circle of Willis
Hypothermia					
Aneurysm					
Light anesthesia	5	5	5	0	5
Deep anesthesia	5	0	0	0	0
A V malformation, parietal	1	1	1	0	
	11	6	6*	0	5
Normothermia					
Local anesthesia					
Subtemporal exposure	1	0	1*	0	1
General anesthesia					
Subfrontal & subtemporal exposures	10	0	6†	0	3

* Postural changes (three cases), dissection of carotid in neck (three cases), dural dissection (three cases), retraction of brain (three cases), but not necessarily the same three cases.
† Dural dissection (three cases), retraction of brain (four cases), and hypothalamus (two cases).

11 patients, 3 were operated upon for an aneurysm, but cardiac changes of minor degree were induced by dissection of the circle of Willis in only 1 of these 3 cases of aneurysm.

With general anesthesia and normal body temperature the monitoring electrocardiogram (EKG) seldom revealed changes in the rate or rhythm of the heart as the result of other surgical maneuvers commonly used during intracranial operations, although cardiac slowing was generally induced on retraction of the brain, especially when portions of the limbic system were retracted, such as the medial temporal,[17] posterior subfrontal, or anterior cingulate cortex.[28,30] Manipulation of the glossopharyngeal (IX) and vagus (X) nerves intracranially also resulted in bradycardia (three of four cases). Manipulation or traction applied to the dura mater, the posterior root of the trigeminal nerve, or (as stated above) segments of the circle of Willis occasionally gave rise to minor cardiac changes, such as distortion of the P wave, an extrasystole, or alterations in the cardiac rate for three to four beats, usually in the direction of slowing. Painful stimuli or blood loss as a rule resulted in tachycardia.

In no case, regardless of body temperature or the type and level of anesthesia, were EKG changes induced by manipulation or dissection of surface vessels of the cerebral cortex (16 cases) or of cranial nerves II, III, IV, VI, VII, and XI, including effective electrical stimulation of the last-mentioned two nerves (Table 2).

Local vasospasm of the circle of Willis, proximal or distal to the aneurysm, was observed on arteriography, as well as at operation, in all but one case in which recent subarachnoid bleeding had occurred. Such local vasospasm was often relieved (see "Comment") as soon as the neck of the aneurysm had been occluded by silver clips. In three cases without an aneurysm temporary local vasospasm of a major basal cerebral artery was induced by surgical manipulation involving the circle of Willis.

The nature and potential significance of these cardiac and vasomotor phenomena will be discussed in the light of abnormal systemic and local factors related to their occurrence.

Material

As indicated in Table 2, these studies were carried out on 30 cases having a variety of lesions, including 13 cases of intracranial aneurysm, 3 of which involved the anterior communicating artery and 10 the internal carotid at the junction of the posterior communicating artery. In all these 13 cases intracranial bleeding had occurred three to six weeks prior to surgery. In 11 cases operation was performed under hypothermia; 10 had aneurysms and 1 an arteriovenous (AV) malformation of the right parietal lobe. In 11 other cases at normal body temperature portions of the circle of Willis were tested for EKG effects, 10 under general anesthesia and 1 with local anesthesia.

Eight aneurysms of the internal carotid artery were operated upon under hypothermia and two at normal body temperature. Two aneurysms of the

anterior communicating artery were operated on under hypothermia and one under general anesthesia at normal body temperature, the latter being included under "miscellaneous" cases in Table 2.

Methods

A. Anesthesia.—After premedication with meperidine (Demerol) hydrochloride 75-100 mg. (h)* and scopolamine hydrobromide 0.4 mg. (h), local infiltration of the scalp with 1% procaine hydrochloride was used in all cases. General anesthesia consisted of intravenous thiopental sodium and intratracheal nitrous oxide-oxygen administration. In most hypothermic cases a Jefferson † automatic respirator was used.

The plane of anesthesia was purposely kept light in the first five hypothermic cases (the only ones in which cardiac arrhythmias were precipitated) because at that time a deep plane of anesthesia was feared in conjunction with hypothermia. A light plane of anesthesia was indicated by motion on painful stimuli, by episodic shivering, and by the electroencephalographic (EEG) pattern. With deeper anesthesia no shivering, motion, or cardiac irregularities occurred. In two of the five cases in which cardiac arrhythmias were precipitated by aneurysmal dissection, the arrhythmias were stopped and no further cardiac irregularities occurred or were evoked after administration of additional thiopental sodium to deepen the plane of anesthesia.

Efforts were made to avoid hypoxia and metabolic acidosis by adequate ventilation. Studies of the blood chemistry, including CO_2 levels, during some of these procedures will be reported separately by Dr. Duncan A. Holaday, assistant professor of anesthesiology, Columbia University College of Physicians and Surgeons.

B. Hypothermia.—After the induction of general anesthesia, cooling was accomplished by placing the patient on a Thermo-Rite † mattress and packing the body with ice cubes. When a temperature of 30 C was reached, the ice was removed. Chlorpromazine, 50-60 mg., was used in the first three cases, in divided doses of 10 mg. Body temperatures were measured by an intragastric Thermistor ‡ attached to an electrical indicating system. The lowest temperature during surgery was 27.2 C, the highest 29.2 C, and the average 28.4 C.

C. Electrocardiogram.—A cardiotachiscope § was constantly used throughout all of the hypothermic and some of the other procedures. In addition, a standard recording EKG apparatus was used in all but the first two hypothermic cases.

The immediate preoperative physical and EKG evaluation of cardiac function proved normal in all but one case. In this case the EKG showed occasional extrasystoles prior to and during, but not after, successful ligation of an internal carotid aneurysm. Another patient, who eventually died ("Comment"), had EKG changes following spontaneous intracranial hemorrhage a week or more before and again after, but not immediately before or after, operation. This was the only case in which the aneurysm had to be packed with muscle.

Cardiac arrhythmia was characterized either by the onset of bradycardia at rates as low as 20, 40, or 60 per minute accompanied by frequent extrasystoles, or by lower nodal tachycardia at rates of 100 to 130 per minute with accentuation of the T wave, depression of the S-T segment, and absence of the P wave, suggesting a nodal rhythm.

D. Blood Pressure.—Constant blood pressure readings were made during hypothermia in two cases by means of a Lilly Capacitometer.‖ In all other cases standard mercury manometer readings were obtained every 60 seconds. In three cases cardiac arrhythmias were usually associated with a blood pressure fall, but in two other cases, including one in which the Lilly manometer was used, the blood pressure was generally unchanged during periods of arrhythmia and alterations of the heart rate.

E. Surgical Maneuvers.—The arteries of the circle of Willis were treated in a similar fashion in each case, i. e., arachnoidal adhesions and old blood clot were gently peeled off the vessels, while in some instances gentle traction, displacement, or pinching of the vessels without occlusion was carried out during their dissection. In the five hypothermic cases subject to arrhythmias, even a light touch applied to the taut aneurysm sac was frequently capable of precipitating bradycardia or an alarming cardiac arrhythmia.

The cranial nerves tested were likewise subjected during their dissection to traction or gentle pressure, while cranial nerve VII was stimulated electrically with sufficient current to produce facial contractions before as well as after removal of four acoustic neurinomas (Table 2).

Report of Sample Case

CASE 2.—Woman, age 23. Aneurysm, saccular, internal carotid artery (Fig. 2). Subarachnoid hemorrhage six weeks prior to admission. Clip

* (h) = hypodermically.

† Air Shields, Inc., Model GH, Hatboro, Pa.

† Thermo-Rite Products Co., Buffalo.

‡ Tele-Thermometer, Yellow Springs Co., Yellow Springs, Ohio.

§ Instrument Laboratories, New York.

‖ Lilly Capacitometer, Model 115A1, Technitrol Engineering Co., Inc., 3212 Market St., Philadelphia.

TABLE 2.—*Number of Cases Showing Cardiac Changes on Testing*

	No. of Cases Tested	Cranial Nerves									
		II	III	IV	VI	V	(Dura)	VII	VIII	IX-X	XI
Hypothermia											
General anesthesia (carotid aneurysms)	8	0	0	0	0	--	3	--	--	--	--
Normothermia											
General anesthesia (miscellaneous)	10	0	0	0	0	--	2	--	--	--	--
General anesthesia (acoustic neurinoma)	4	--	--	--	--	--	0	0	0	3	0
General anesthesia (tic douloureux)	4	--	--	--	--	2	1	--	--	--	--
Local anesthesia (subtemporal)	1	0	0	0	0	--	1	--	--	--	--
		0	0	0	0	2	(7)	0	0	3	0

occlusion of aneurysm under general anesthesia and hypothermia.

Preoperative EKG.—Normal. Heart rate 70 a minute. P-R interval 0.18 second.

Operation (Nov. 15, 1954).—Under conditions of relatively light general anesthesia and hypothermia as described, the carotid arteries were isolated in the neck and ligatures passed loosely beneath them. Temporal craniotomy revealed moderately increased intracranial pressure, requiring resection of part of the middle and inferior temporal gyri in order to expose the site of the aneurysm without undue brain retraction. The large saccular aneurysm was then dissected free of organized blood clot, the adherent oculomotor nerve, and the free margin of the tentorium. The neck of the aneurysm was then successfully occluded with aneurysm clips (Fig. 3).

Cardiovascular Changes During Procedure.

After induction of anesthesia, ice was applied at 9:05 a. m. At 12:30 p. m. brief cardiac arrhythmia coincided with dissection about the carotid bifurcation in the neck: temperature 27.6 C; B. P. 80/70; pulse 60 a minute. A postural change, consisting of elevation of the head at 1:00 p. m., led to cardiac arrhythmia and slowing to 50 a minute for nine minutes, with a steady B. P. of 90/60. At 1:11 p. m., dural opening again led to the same type of cardiac arrhythmia: B. P. 80/62; T. 27.3 C. Traction on the dural flap five minutes later, however, induced no further EKG changes. On resection of temporal lobe tissue, at 1:45 p. m., with some blood loss, the pulse rate abruptly increased from 50 to 100 a minute, with a brief drop in blood pressure.

Lower nodal tachycardia, with spreading of the QRS complex, or ventricular tachycardia (Fig. 4), occurred upon dissection of the aneurysm, at 1:52 p. m. On exposure of the neck of the aneurysm, at 2:10 p. m., the pulse rate fell abruptly from 108 to 48 a minute, at a steady B. P. of 90/60. Ten minutes later the pulse rate was 80 a minute. When further dissection of the aneurysmal sac was cautiously and gently pursued from 2:30 to 3:00 p. m., the pulse fell from 80 to 48 a minute, as in a similar case (Fig. 5). After intravenous administration of 2.0 cc. of thiopental sodium, at 3:00 p. m., normal sinus rhythm was restored, and no further cardiac irregularities occurred.

Cardiac arrhythmia occurred briefly on dissection of the carotid artery in the neck, on a postural change of the head, on opening the dura, and on dissection of the aneurysm and adjacent vessels. Abrupt brief

Fig. 2 (Case 2).—Aneurysm of right posterior communicating artery at carotid junction.

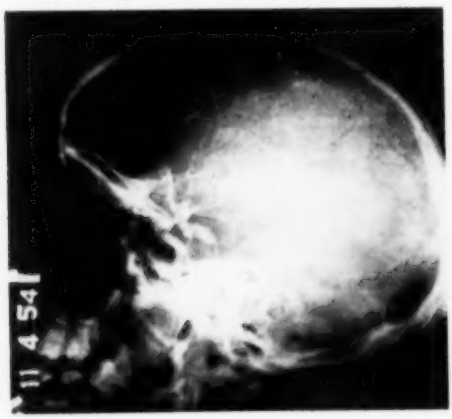
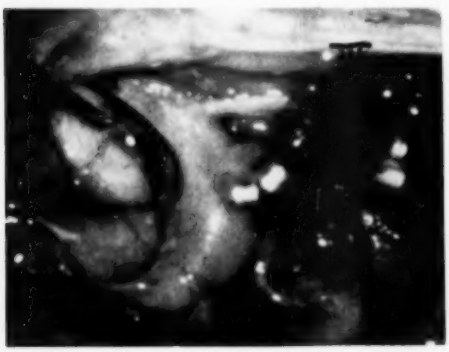


Fig. 3 (Case 2).—Operative photograph of aneurysm occluded by four silver clips. *A* indicates clipped aneurysm; *B*, brain; *C*, site of clot; *T*, tentorium, and *III*, third nerve.



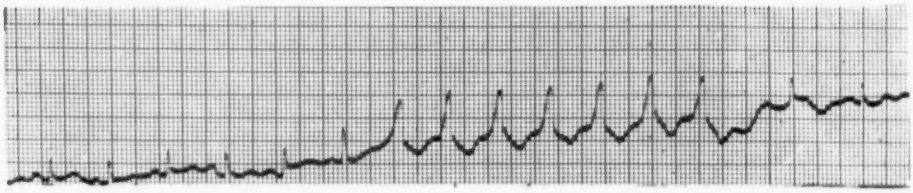


Fig. 4 (Case 2).—Cardiac arrhythmia: Lower nodal or ventricular tachycardia with alterations of QRS complex occurring upon dissection of aneurysm of circle of Willis. Hypothermia.

bradycardia occurred on exposing the aneurysmal neck, as it had during its dissection. After additional, deeper anesthesia normal sinus rhythm was restored and maintained.

In summary, a variety of stimuli, including those affecting the aneurysm and adjacent portions of the circle of Willis, altered the rate or rhythm of the heart in this case, as in four similar cases of this series.

Comment

Alterations in cardiac rate or rhythm may result from a variety of neurogenic stimuli, both central and peripheral in origin,[4,10] including stimuli applied during surgery to major arteries of the body. However, there is little evidence that mechanical stimuli applied to the basal cerebral arteries may also alter cardiac activity. The object of this communication, therefore, is to indicate that under certain circumstances arteries of the circle of Willis may react in much the same manner as do major arteries elsewhere in the body, both as to remote (cardiac) and to local (vasospastic) reflex responses.

In line with the first part of this concept is a case cited by Levine,[22] in which "changes in the RS-T segment, as well as in the T wave [might] develop for reasons not entirely clear at this time, in association with disease of the central nervous system, [leading to] the diagnosis of myocardial infarction. . . . Postmortem exam-

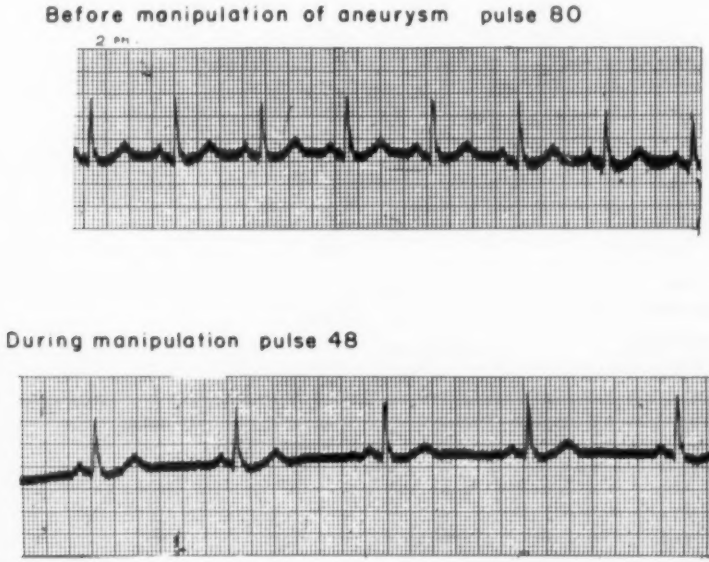


Fig. 5 (Case 3).—Bradycardia, from a rate of 80 to 48 a minute, on gentle dissection of aneurysm of internal carotid artery, with no alteration of blood pressure. Hypothermia.

ination showed a ruptured aneurysm of the circle of Willis but on meticulous microscopic examination no evidence of myocardial infarction or of pericarditis." Another neurosurgeon,[20] moreover, has recently informed me of a case in which fatal ventricular fibrillation was initiated at the moment of dissecting (without rupturing) an intracranial carotid aneurysm under hypothermia.

In our cases of preoperative myocardial damage, blood pressure changes and the actual degree of hypothermia were apparently not significant factors related to the onset of cardiac arrhythmia. For example, all but one of our patients had a normal EKG immediately before operation. In two cases, moreover, the blood pressure was not altered during episodes of bradycardia or cardiac arrhythmia, and, finally, there was no correlation between registered body temperatures and the occurrence or character of induced cardiac irregularities.

It therefore appeared that other factors must be considered, such as two general, or systemic, factors which evidently rendered the heart unusually sensitive to extraneous stimuli in the first five cases of aneurysm, namely, (1) hypothermia, in conjunction with (2) a relatively light plane of anesthesia. Supporting this thesis are the pronounced cardiac arrhythmias, similar to those observed in our five cases, which also occurred under hypothermia and relatively light anesthesia, indicated by shivering, during the intracranial operations so carefully studied by Lougheed et al.[23]

While cardiac activity may be altered by toxic or metabolic effects of anesthetic agents,[10] including metabolic acidosis, an insufficient depth of anesthesia may also lead to cardiac irregularities, as the result of inadequate nerve or synaptic blocking, which fails to protect the heart during surgery from impulses reaching it from nerves, viscera, or major blood vessels. It now appears that stimulation of basal cerebral arteries may also initiate abnormal cardiac effects if anesthetic blocking is inadequate, especially when the heart is already rendered abnormally sensitive to extraneous stimuli as the result of hypothermia.

Adequate anesthesia may be provided by a "general," diffusely acting anesthetic agent, such as thiopental sodium, or by drugs, such as chlorpromazine or trimethaphan camphorsulfonate (Arfonad), having a more specific blocking action on certain parts of the nervous system, such as central or peripheral components of the sympathetic system, respectively.

Progressive body cooling, moreover, may lead not only to progressive cardiac slowing but also to severe spontaneous[27] or readily induced cardiac irregularities.[38] Such effects have been attributed to the direct influence of cooling upon the heart[9] and to other effects of cooling, such as increased neural activity and increased reflex discharge within the spinal cord,[3,8] enhanced synaptic transmission, and release of epinephrine.[21] Any or all of these effects, in other words, may contribute to abnormal cardiac action in cases of hypothermia.

A local factor to be considered with regard to the cardiac changes so readily evoked from manipulations of the circle of Willis in the first five aneurysm cases is the possibility that local perivascular extravasation of blood from the recently ruptured aneurysm has led to a state of unusual local vascular irritability. This possibility is suggested by the ease with which cardiac effects followed even minimal mechanical stimulation of arteries so affected, and the fact that local or segmental vasospasm is so often associated with a recently ruptured aneurysm.[14,18,35]

Such arterial narrowing of the type illustrated in Figure 6 is probably often correctly considered to represent a state of vasospasm, rather than a mechanical "depulsator effect" of the aneurysm,[16] since the reduction of arterial caliber is usually present for only a few weeks after recent bleeding, when the narrowing or spasm generally disappears, even though the aneurysmal sac is still present and open. More-

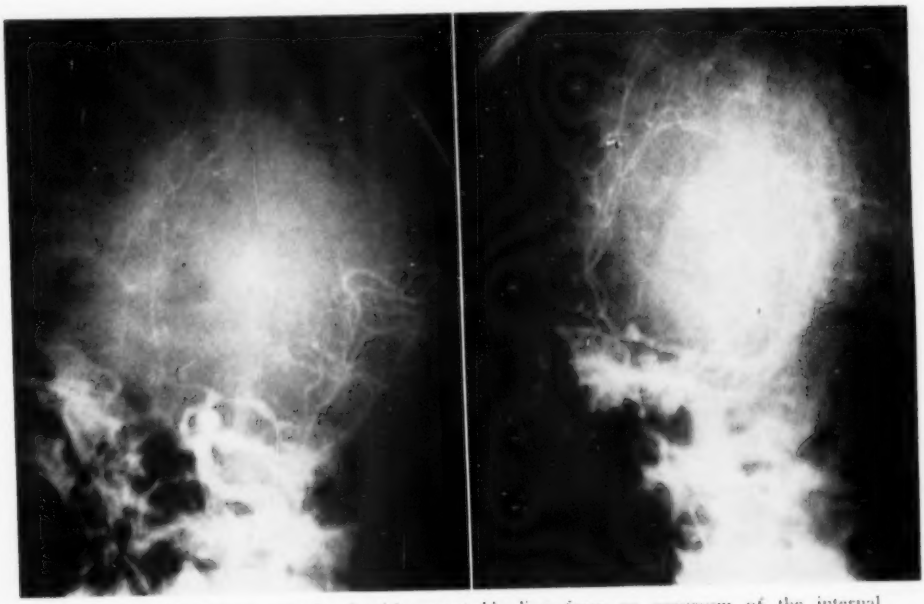


Fig. 6.—Vasospasm associated with recent bleeding from an aneurysm of the internal carotid artery (left). Note marked vasospasm of irregular character affecting the left middle and anterior cerebral arteries and absence of spasm on the opposite side (*R*), with earlier and ampler filling of the right anterior and middle cerebral arteries.

over, in the cases in this series in which narrowing of the internal carotid artery was demonstrated, and regardless of whether the narrowing was proximal or distal to the aneurysm, the narrowed lumen usually resumed its full, and apparently normal, caliber after the aneurysmal neck was ligated.

While these observations alone do not entirely rule out a depulsator effect, it was felt that any such purely mechanical effect of an aneurysm can be excluded because narrowing of the carotid lumen has been seen to persist during temporary trapping of a carotid aneurysm and the adjacent narrowed portion of the carotid artery. Not until the neck of the now partly collapsed aneurysm was occluded by a permanent clip did the narrowed carotid artery assume a larger, and apparently normal, size. It seems probable, therefore, that clip obliteration of a recently ruptured aneurysm removes a source of local irritation serving to maintain adjacent arterial segments in a state of vasospasm.

While the mechanism of this phenomenon is a matter of speculation, it can be assumed that the presence of recent hemorrhage within and around the walls of an aneurysm (Fig. 7) may render its intrinsic nerves or musculature hyperirritable, a state which, in turn, may spread along local ramifications of these vasomotor nerves or muscles in a manner that depends on the extent of local pathology and factors of individual vasomotor suspectibility. With regard to such a theory, experimental data indicate that chemical, mechanical, or electrically induced stimuli may result in segmental or diffuse narrowing of cerebral arteries,[15,29] even though these effects may be inconstant.[31] Such experimental findings thus tend to substantiate clinical observations indicating that segmental vasospasm,[2,14,35] perhaps influenced by individual variations in vascular response,[1,39,42] may affect the cerebral arteries in man. In this regard, it may also be noted that major basal cerebral arteries may react to mechanical stimuli at operation by prompt local vasospasm, as

Fig. 7.—Photomicrograph of ruptured aneurysm of posterior communicating artery showing hemorrhage (*H*) within wall of aneurysm (extreme right) and stretched thin-walled sac. *N*, normal artery at left.

may arteries elsewhere in the body. An example of this is our first case, in which manipulation of the posterior communicating and internal carotid arteries, preparatory to wrapping a junctional aneurysm with a Vinyon [5] strip, caused these arteries to become visibly contracted until completion of the procedure.

It has been suggested that cerebral or peripheral arteries already rendered abnormal by local or systemic disease may thereby become unusually susceptible to added insults.[1,39,42] Moreover, cerebral arteriography may lead to temporary hemiplegia,[37] apparently due to vasospasm, as judged by a lower incidence of such complications when general anesthesia [34] or a local pericarotid procaine block is used.[18] It is evident, too, despite considerable controversy,[13,26,42] that stellate ganglion block or stellectomy sometimes improves the cerebral blood flow [36] sometimes relieves hemiplegia attributed to cerebral vasospasm and may abolish responses of the cerebral circulation to extraneous stimuli.[7]

Altogether, these data and the case studies reported suggest (1) that the major basal cerebral arteries in man may react in a similar fashion as peripheral arteries elsewhere in the body; (2) that cerebral vasospasm is a real phenomenon; (3) that cerebral arterial vasospasm may occur as the result of an acute pathological process affecting that artery, and (4) that cerebral arteries affected by an acute abnormal pathological process, such as perivascular hemorrhage, may thereby become locally hyperirritable, and thus unusually prone to local, and sometimes remote, vasospasm and unusually sensitive to the effects of additional insult.

Innervation of Cerebral Arteries.—Consideration of the innervation of the cerebral arteries is pertinent to this discussion, since it is possible that cerebral vasospasm is not solely due to contraction of arterial constrictor muscles but may be initiated, or at least propagated, by the nerve supply of the affected vessels.

Data on human and animal material indicate that the vessels of the circle of Willis are innervated by a continuation of the cervical sympathetic system by way of the internal carotid artery and cavernous plexus and by posterior connections with cervical sympathetic elements coursing along the vertebral and basilar arteries.[19,24,25,40] Nerve branches are also said to join the intracranial portion of the carotid system via the greater superficial petrosal nerve,[11] the caroticotympanic plexus,[24] and cranial nerves IX and X.[12,24] While vasomotor nerve twigs have also been attributed to other cranial nerves, the work of Ray and Wolff [33] and the observations of this series of cases tend to minimize their significance.

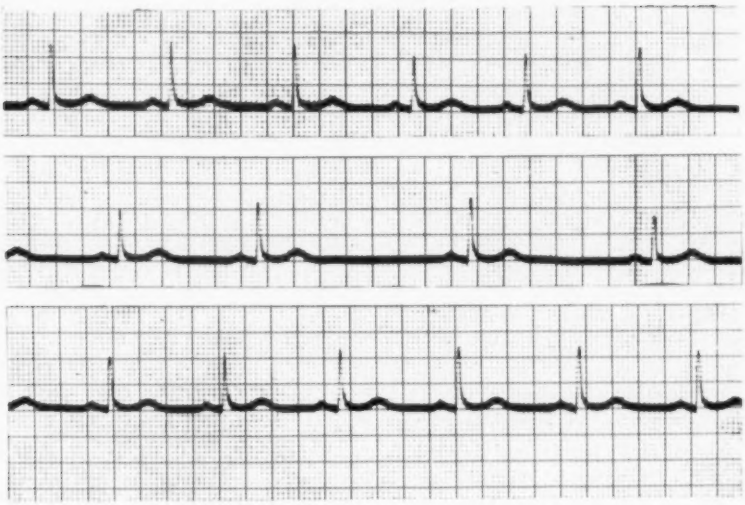


Fig. 8 (Case 14).—Trigeminal root traction: bradycardia (middle strip) during traction. General anesthesia without hypothermia.

Ray and Wolff [33] believe that the sensory innervation of the major cerebral arteries is essentially as follows: infratentorially, from cranial nerves IX and X and the upper two cervical sensory roots, and supratentorially, from the first division of the trigeminal nerve. The latter view is substantiated by the frequency of pain referred to the ipsilateral eye and side of the forehead in the presence of an aneurysm of the carotid or posterior communicating artery, and by the fact that pain referred to this region was induced in the case of psychomotor epilepsy (of this series) by traction on the posterior communicating artery. In this case gentle traction on this artery resulted in bradycardia, whereas firmer traction, sufficient to induce mild pain about the eye, resulted in tachycardia.

The fact that bradycardia resulted from surgical manipulation of affected parts of the circle of Willis, as well as of the trigem-

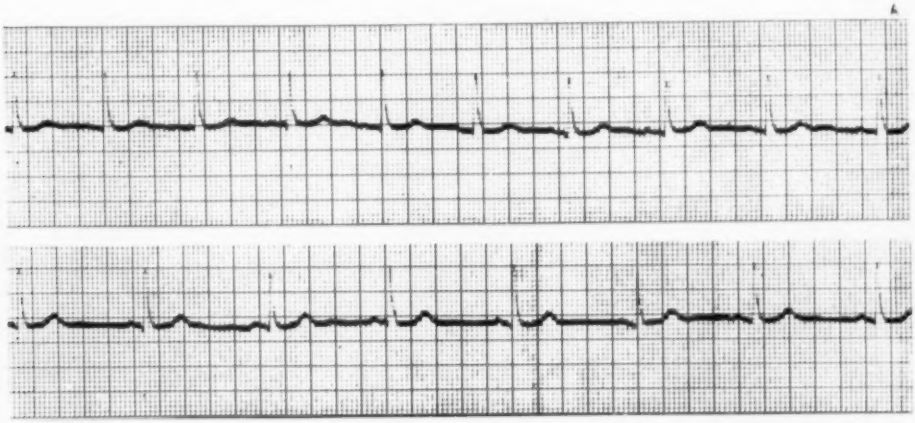


Fig. 9.—General anesthesia. Bradycardia (lower strip) on gentle pressure upon cranial nerves IX and X.

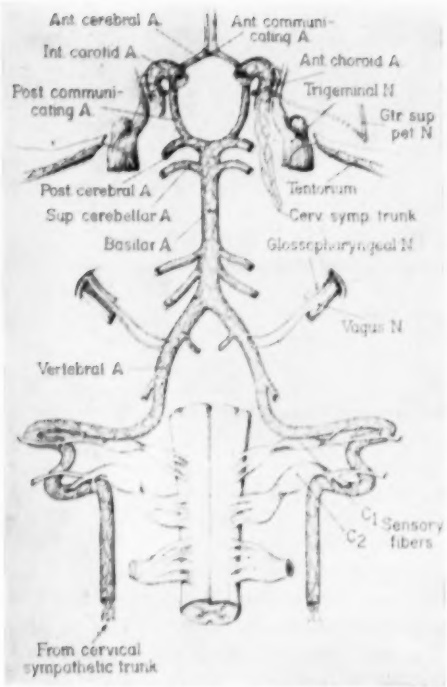
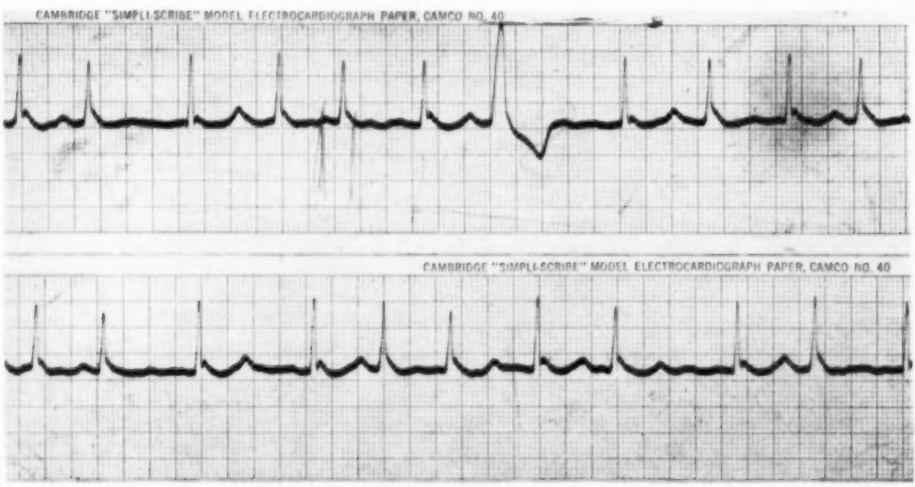


Fig. 10.—Innervation of the circle of Willis and vertebral arteries in man (schematic).

inal (Fig. 8) or glossopharyngeal and vagus nerves (Fig. 9) suggests that the major basal cerebral arteries may be innervated (*a*) in part by cranial nerves IX and X or (*b*) by trigeminal fibers which relay impulses to the nuclei of cranial nerves IX and X, as in the oculocardiac reflex. It is not unreasonable to implicate nerve IX as well as X in relation to cardiac effects, since carotid sinus[39] and glossopharyngeal neuralgia reflex effects have both been known to cause cardiac arrest.[32] The tachycardia induced in some of our cases, on the other hand, may indicate activation of the sympathetic system either centrally or directly.

A schematic summary of the nerve supply of the circle of Willis is shown in Figure 10.

Finally, it is evident that stimulation of the dura, including the middle meningeal artery, and the tentorium failed to evoke EKG changes as readily as subsequent dissection of the basal arteries or an aneurysm of the circle of Willis, and that dissection of cranial nerves II, III, IV, and VI (10 cases) and cranial nerve XI (4 cases) or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CAMBRIDGE "SIMPLI-SCRIBE" MODEL ELECTROCARDIOGRAPH PAPER, CAMCO NO. 40

Fig. 11 (Case 8).—Distorted extrasystoles, as illustrated near center of upper tracing, occurring three to four times per minute prior to occlusion of aneurysm of the anterior cerebral artery. Lower tracing, free of such extrasystoles, is characteristic of EKG following clipping of aneurysm.

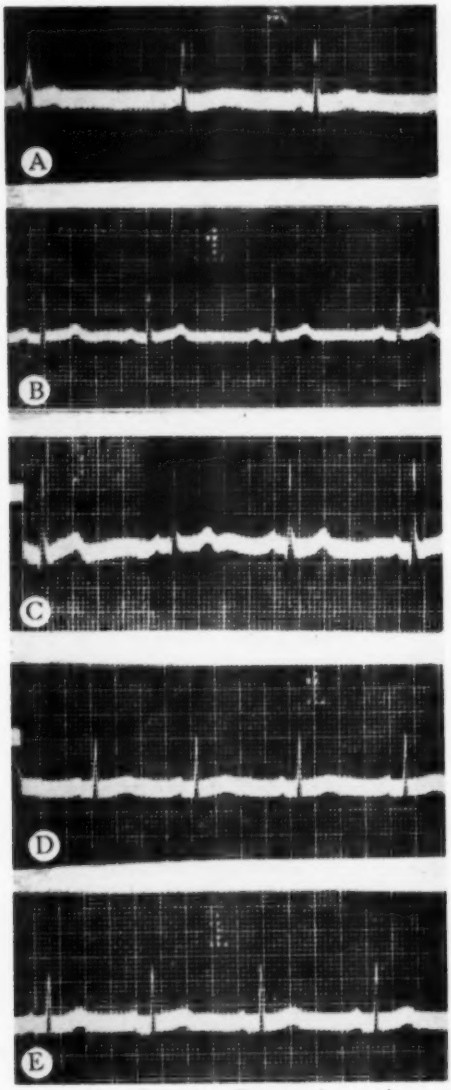

Fig. 12 (Case 4).—Preoperative and postoperative EKG records (Lead 1). *A*, abnormal EKG (Sept. 19), shortly (about one week) after rupture of the aneurysm, showing low T waves and frequent ventricular and nodal premature beats. *B*, return to normal prior to (Oct. 17) and, *C*, after (Oct. 26) operation. *D*, reappearance of an abnormal EKG pattern (Oct. 31) after signs of recurrent bleeding (flap tension) with nuchal rigidity. T waves flat or inverted Leads I, aV_L and V_5, only to resolve *E* despite persisting increased intracranial pressure (Nov. 3), with recovery from signs of bleeding.

These observations suggest the possibility that rupture of an aneurysm of the circle of Willis and/or perivascular hemorrhage may result in transitory reflex cardiac effects.

electrical stimulation of cranial nerve VII (4 cases) failed to induce EKG changes (Table 2), although gentle pressure on cranial nerves IX and X in cases of an acoustic neurinoma (3 of 4 cases) led to temporary bradycardia (Fig. 9).

From all these data the impression is gained (*a*) that in susceptible cases extraneous stimuli are more apt to provoke EKG changes when applied to the major basal cerebral arteries than to other intracranial structures, such as the cortical vessels and certain cranial nerves, and (*b*) that systemic factors, such as the level of anesthesia, lowered body temperature, and latent cardiovascular pathology, may trigger the heart or render it more susceptible to irregularities from adventitious stimuli, including stimuli applied to the basal cerebral arteries of the circle of Willis. It is possible that these cardiac effects represent a direct neurogenic reflex phenomenon mediated by the trigeminal-vagal pathway. It is also possible that cardiac changes from manipulation of the circle of Willis may reflect hypothalamic effects,[40] due to a local neurogenic reflex mediated either by the intrinsic nerves of the blood vessels or by temporary circulatory changes within the hypothalamus secondary to the manipulation of the circle of Willis. However, the speed with which these cardiac effects occur suggests a neurogenic reflex effect rather than a circulatory phenomenon as their cause.

Some of these observations suggest the possibility that the occurrence of local pathological changes affecting the circle of Willis may even initiate abnormal local vasomotor reflexes capable of altering the cardiac rate or rhythm, as in Case 8 (Fig. 11) or Case 4, as indicated by the abnormal preoperative EKG (Fig. 12), shortly after the initial subarachnoid hemorrhage. The EKG later became normal in Case 4 and was still considered normal directly after operation for muscle-stamp packing of a posterior communicating aneurysm, but again revealed abnormalities when recurrent bleeding subsequently occurred.

As to the immediate clinical significance of these data, it is obviously important both for theoretical and for practical reasons that a careful preoperative study of cardiac function be done, especially when hypothermia is to be used, since manipulation of an aneurysm or adjacent vessels of the circle of Willis in a hypothermic patient may induce a vasocardiac reflex leading to serious, and even fatal, cardiac arrhythmias, as indicated by one unpublished report [20] of fatal ventricular fibrillation induced by dissecting an aneurysm of the circle of Willis during hypothermia. Deeper anesthesia, other techniques of anesthesia,[6] or the use of appropriate blocking agents might well have prevented such accidents.

Of theoretical interest is the fact that cerebral vasospasm of the circle of Willis and its ramifications may occur as a result of a local vascular insult, whether hemorrhagic or mechanical, leading to local vasovasal reflex effects mediated by the intrinsic nerve supply of the cerebral arteries. Finally, it seems possible that alterations in the electrocardiogram may sometimes be precipitated as the result of an acute pathological process affecting vessels of the circle of Willis.

Summary and Conclusions

Electrocardiogram (EKG) studies were made during 30 intracranial operations under various conditions of anesthesia and body temperature.

Alterations in the cardiac rate and/or rhythm were induced in 9 of 22 cases by operative manipulation of major basal cerebral arteries comprising parts of the circle of Willis.

The most pronounced cardiac changes (arrhythmia) appeared on dissecting an aneurysm or adjacent arterial segments of the circle of Willis when a combination of relatively light general anesthesia and hypothermia was used (five cases). With deeper anesthesia and hypothermia (five additional cases) no EKG changes occurred.

Less pronounced EKG changes occurred when homologous arteries were dissected under local (one case) or general anesthesia (two cases).

Other types of surgical manipulation that occasionally resulted in transitory cardiac changes included postural changes and dissection of the carotid arteries in the neck under hypothermia, and traction or cauterization applied to the dura mater, the tentorium, or the brain, with or without hypothermia. Similar stimuli applied to cortical arteries did not evoke cardiac changes.

Stimulation of cranial nerves V, IX, and X gave rise to EKG changes in some cases, but not stimulation of cranial nerves II, III, IV, VI, VII, VIII, or XI.

Cardiac responses to stimulation of basal cerebral arteries were apparently influenced by the effects of systemic and local factors.

A. *Systemic Factors*
   1. Anesthesia
   2. Hypothermia
   3. Cardiovascular status

B. Local Factors

Local vascular pathology, such as the presence of an aneurysm, and recent perivascular hemorrhage, serving to render the affected arteries unusually sensitive to adventitious stimuli.

Vasospasm of the major cerebral arteries appears to be a real phenomenon, and, for reasons discussed in the text, it seems probable that a focal vascular lesion may initiate and perpetuate a state of vasospasm in adjacent arterial segments by means of a vasovasal reflex.

The innervation of the circle of Willis is discussed. Sensory innervation of the circle of Willis apparently stems predominantly from cranial nerve V, and possibly cranial nerves IX and X, and autonomic innervation, from the cervical sympathetic system. An intrinsic segmental innervation of these arteries is suggested by local vasospasm (arteriographic and operative observations).

The possibility that cardiac abnormalities may be initiated spontaneously by a serious intracranial vascular lesion is advanced in the light of the EKG changes associated

with intracranial bleeding on two occasions in Case 4, and by postoperative EKG improvement in other cases.

Vasocardiac reflexes induced by surgical manipulation of the circle of Willis, under certain conditions of hypothermia and a relatively light plane of anesthesia, may lead to serious cardiac arrhythmias. This phenomenon may account for some reported cases of fatal ventricular fibrillation. Deeper anesthesia or suitable blocking drugs may prevent such effects.

A potentially powerful nerve supply, capable of exerting important local and remote effects, innervates the circle of Willis. Under certain circumstances vasovasal and vasocardiac reflexes may originate in the circle of Willis.

Medical consultants conducted the preoperative cardiac work-up of these cases, and members of the service of anesthesiology cooperated effectively in this study. Dr. John H. Laragh, instructor in medicine, and Dr. Duncan Holaday, director of research in anesthesiology, read and criticized the manuscript.

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Changes in the Blood-Brain Barrier After Exposure of the Brain

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Prolonged exposure of the brain, such as occurs during neurosurgical procedures, frequently results in cerebral swelling and cerebral edema. These changes are generally attributed to disturbances in the cerebral circulation (Cannon[1]; Obrador and Pi-Suñer[2]; Evans and Scheinker,[3] and Prados, Strowger, and Feindel[4,5]). Some investigators have been concerned with the permeability of the "blood-brain barrier" in these conditions. By injecting trypan blue intravitally, Prados et al.[4,5] found macroscopically visible staining after exposure of the brain, particularly noticeable in the gray matter of the exposed areas. These experiments showed that cerebral vessels undergo an increase in permeability to trypan blue when the brain is exposed to air. In contrast to these observations, Apfelbach,[6] Bonvallet and Le Beau,[7] and Obrador and Pi-Suñer[2] failed to observe such an increase in trypan-blue permeability in their experiments on cerebral edema resulting from exposure or from other experimental procedures.

As Rodriguez[8] has pointed out, trypan blue has certain disadvantages for studies involving the blood-brain barrier which are not present when aminoacridine dyes are used. By using these dyes, Rodriguez has been able to determine the precise histologic localization of the blood-brain barrier, i. e., the blood vessel endothelium. These compounds have the unique property when injected intravenously of staining in vivo the nuclei of all the cells in the organism save those of the central nervous system, where neither parenchymal or vascular cells are stained.* The detection of these dyes on a cellular level is possible because of their fluorescence in near-ultra violet light. Subarachnoid administration results in nuclear staining of the cells of the central nervous system, including the vascular endothelium. It is apparent that the endothelium constitutes the blood-brain barrier which prohibits entrance of these dyes into the central nervous system. In view of the observations of Rodriguez, it appeared of interest to examine whether actual changes in the permeability of the endothelium could be directly demonstrated by aminoacridine compounds after exposure of the brain.

Materials and Methods

Adult male rabbits were used. The skull was opened by trephining under aseptic conditions an area half an inch in diameter in the left parietal bone. Two series of animals were used. In one series of animals the dura was gently perforated and a piece of dura slightly smaller than the size of the opening in the skull was removed. In the second group the dura was left intact. In both series the skin was closed with nonabsorbable surgical (silk) sutures after an exposure of approximately 45 minutes. Tissues were removed under pentobarbital (Nembutal) anesthesia at the following postoperative periods: ½, 2, and 12 hours, and 1, 2, 3, 7, 14, and 21 days. One to four animals were used for each time interval. The

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* Some exceptions are the area postrema, neurohypophysis, intracolumnar tubercle, etc., where the vessels apparently have permeability properties different from those of the rest of the central nervous system.

tissues were taken not only from the site of exposure but also from other areas of the cortex.

Proflavine hydrochloride (3,6-diaminoacridine hydrochloride) or acriflavine, a mixture of proflavine and 3,6-diamino-10-methylacridinium chloride, dissolved in saline was injected into the marginal vein of the ear approximately an hour before removing the tissues. An exception was the one-half hour interval, where the dye was injected half an hour before killing the animal. The amounts used were 15 mg. of proflavine and 25 mg. of acriflavine per kilogram of body weight. At later phases of the experiments, proflavine was used almost exclusively, because of its stronger fluorescence. The tissues were frozen-dried and embedded in paraffin (in vacuo). Further processing and methods of observation were carried out according to the methods of De Bruyn, Robertson, and Farr.[8] Tissues from animals, injected as described above, but with unexposed brain, served as controls. In addition to observations on the fluorescent preparations, studies were made of sections stained with Ehrlich's hematoxylin and eosin.

Results

After the skull was trephined, swelling of the brain was revealed, which was severest when the dura was removed. This swelling became evident a few minutes after the skull was opened and reached a maximum at the three day postoperative interval. After this time there was usually a regression of the swelling. This regression at still later stages (7-10 days) was enhanced by connective tissue formation resulting from regenerative processes occurring over the region of the exposed brain.

Examination of brain tissue obtained from control animals injected intravenously with acriflavine did not reveal any nuclear fluorescence in the cerebral cortex. Blood vessel identification was occasionally possible when, in some preparations, erythrocytes showed a faint fluorescence.

Dura Removed.—Tissues taken from animals killed one-half hour postoperatively did not differ from the control tissue in fluorescence. In preparations taken at later intervals in the region of exposure, two types of tissue localization of the nuclear staining were observed: (*a*) staining of the endothelial nuclei of the blood vessels and (*b*) staining of the parenchymal nuclei. No systematic study was made of the staining of other areas. It was evident, however, that the staining was not limited to the site of exposure but occurred also in adjacent areas. The staining diminished considerably as the distance from the site of exposure increased. Both types of tissue localization occurred in the gray matter. In the white matter only endothelial fluorescence was found, and invariably to a much slighter degree than in the gray matter.

In tissues removed two hours after exposure, the nuclei of the capillary endothelium are clearly stained. In some instances it appears that the intranuclear dye is present in a punctiform fashion (Fig. 1). The nuclei of the parenchyma are only faintly fluorescent.

Twelve hours after operation, there is an intense staining of all endothelial nuclei, including those of the larger vessels. Parenchymal nuclei in the vicinity of the blood vessels are stained more strongly than at the two-hour interval. Nuclei farther away from the blood vessels stain faintly. The intranuclear dye is present in a pattern corresponding to the distribution of chromatin (Fig. 2). At this time the nuclear fluorescence of the large arterioles indicates that they are permeable to the dye, although the parenchymal nuclei surrounding these blood vessels apparently do not have as yet a sufficient dye concentration to fluoresce. At 24 hours the results are essentially the same, but with increased brilliance in fluorescence and a spread of the staining in the parenchyma so as to include most of the nuclei of the tissue.

On the third day after operation, the staning of the endothelial nuclei is most intense (Fig. 3). Parenchymal nuclei, although clearly stained, are less intense than the vascular endothelium. The cytoplasm stains faintly.

The tissue at the seventh postoperative day generally shows a less intensive nuclear fluorescence than at the three-day interval (Fig. 4). The endothelial nuclei stain more

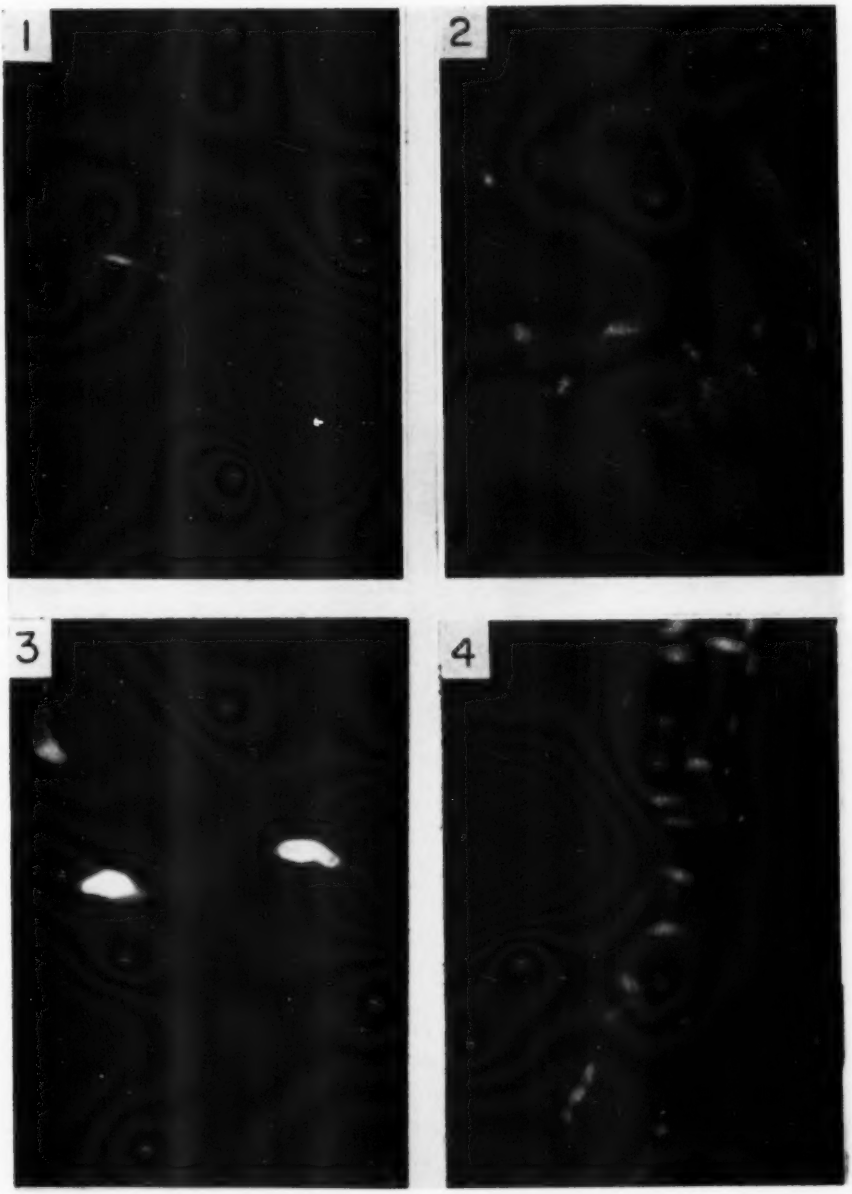

Plate I

Fig. 1.—Cortex, rabbit, dura removed. Proflavine HCl, intravenous injection. Two hours after exposure of the brain. Note staining of the capillary endothelial nuclei. Magnification × 265.

Fig. 2.—Cortex, rabbit, dura removed. Proflavine HCl, intravenous injection. Twelve hours after exposure of the brain. Nuclei of the endothelial and parenchymal cells are stained. Magnification × 256.

Fig. 3.—Cortex, rabbit, dura removed. Acraflavine HCl, intravenous injection. Three days after exposure of the brain. The endothelial nuclei are stained intensively. The parenchymal nuclei show less intense staining. Magnification × 265.

Fig. 4.—Cortex, rabbit, dura removed. Proflavine HCl, intravenous injection. Seven days after exposure of the brain. The endothelial nuclei of the walls of an arteriole are stained. Note that the endothelial staining is less intense than at the three-day interval. Magnification × 265.

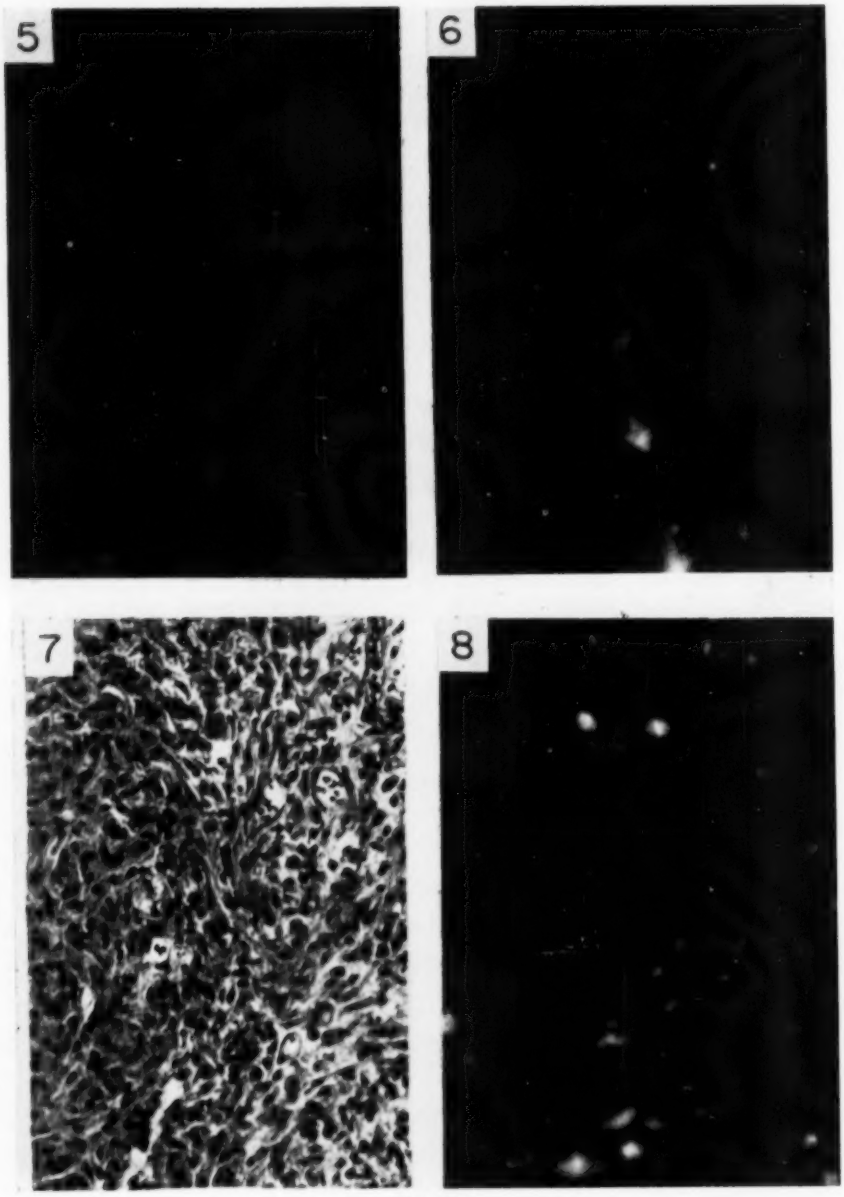

Plate II

Fig. 5.—Cortex, rabbit, dura removed. Proflavine HCl. Intravenous injection. Fourteen days after exposure of the brain. The staining of the endothelium is now very faint. Magnification × 265.

Fig. 6.—Cortex, rabbit, dura intact. Proflavine HCl, intravenous injection. Two days after exposure of the brain. The staining of the endothelial nuclei is much fainter than that of a comparable interval where the dura is removed. Magnification × 265.

Fig. 7.—Spontaneous meningioma present at the site of operation. Hematoxylin and eosin stain; × 235.

Fig. 8.—Same meningioma as that illustrated in Figure 7. Proflavine HCl, intravenous injection. The in vivo nuclear staining of the tumor is much more intense than that of the parenchymal cells outside of the tumor. Magnification × 265.

strongly than the parenchymal nuclei, although occasionally an island of intensely staining nuclei may be found. An incidental finding in this material was a small meningioma (Fig. 7). This tumor shows an intensive nuclear staining (Fig. 8). At the periphery of the tumor, there is a gradual fading of the fluorescence into an intensity at which it generally occurs in the exposed tissue at this postoperative time interval. White matter located under the tumor also shows a strong staining of the oligodendroglial nuclei.

In 14- and 21-day preparations there is a progressive decrease in the intensity of the staining of the endothelial and parenchymal nuclei. In the 14-day animal there is little staining of the nuclei outside the blood vessels, while the endothelium itself is quite faint (Fig. 5). At these intervals there is a growth of connective tissue over the exposed area, which fluoresces intensively as compared with the fluorescence in the nervous tissue itself.

At 21 days there is no staining of the parenchymal nuclei and the staining of the endothelial nuclei has diminished to such an extent that it is only occasionally detectable. In most cases there is no staining at all.

Dura Intact.—The sequence of events regarding the in vivo nuclear staining in this series is essentially similar to that described for the animals without dura. In general, however, the staining appears later and is much fainter and less extensive than when the dura was cut. The greatest changes were again observed at the three-day postoperative period.

By 12 hours after operation there is only a mild staining of endothelial nuclei of the blood vessels. After two days endothelial nuclei stain more strongly and a faint staining of the parenchymal nuclei occasionally occurs (Fig. 6).

Three days postoperatively staining of the endothelial and parenchymal nuclei is stronger than before. However, the parenchymal nuclei are much less intensely stained than those of the endothelium. By seven days the parenchymal nuclei no longer fluoresce and only endothelial nuclei stain faintly. All later preparations were indistinguishable from those obtained from animals injected with dye, but of which the brain was not exposed.

Histologic Observations.—The histologic examination of material stained with hematoxylin and eosin revealed definite pathologic changes. There was an increase in the fluid space between the blood vessel wall and the neural matrix, which became visible at 12 hours. Later, at about 24 to 48 hours, spaces developed between the cell wall and the neural matrix (perineuronal space). These two conditions resulted in a sponge-like appearance of the neural matrix suggestive of edema. Congestion of blood in dilated blood vessels was commonly observed in the veins. Erythrocytes occurred frequently outside the blood vessels, but no hemorrhages, with discontinuity of the blood vessel wall, were seen.

Although the changes are essentially the same in the two series, they occur to a milder degree in the animals with intact dura. In addition, the degree to which these changes occur seems to depend on the length of time after operation. They are most striking at the three-day interval (Figs. 9 and 10). In the seven-day preparation there is a definite diminishing of the perineuronal and perivascular spaces. Blood vessels appear fairly normal in size. The 14- and 21-day preparations are indistinguishable from the control tissue.

Comment

The present findings show that exposure of the brain results in an increase in the permeability of the blood-brain barrier, i. e., of the vascular endothelium. This is evident from the fact that the vascular endothelium, as well as the cells of the nervous parenchyma, which under normal conditions do not stain after intravenous injection with aminoacridines, shows in vivo nuclear staining after exposure of the brain. In addition, accumulation of fluid occurs in the peri-

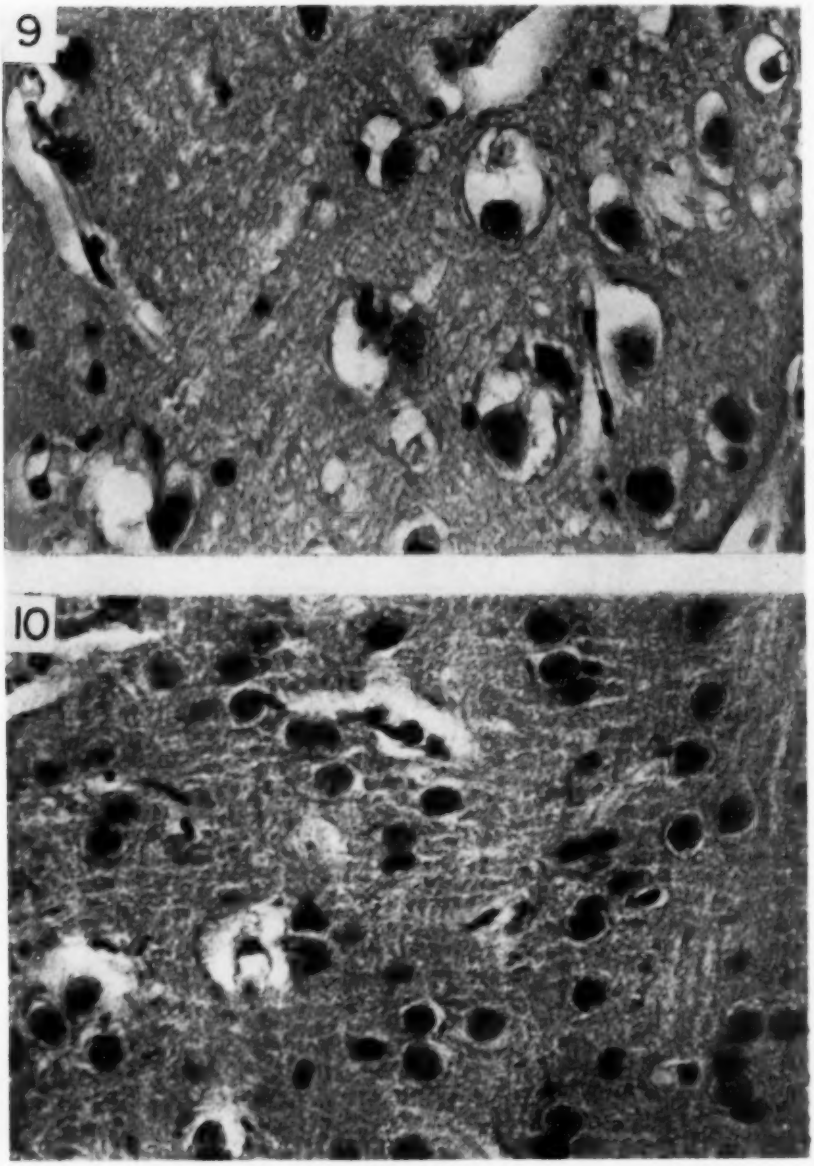

Plate III

Fig. 9.—Cortex, rabbit, dura removed. Three days after exposure. Note the large perivascular and perineuronal spaces, giving the cortex a "spongy" appearance typical of cerebral edema. Hematoxylin and eosin stain; magnification × 625.

Fig. 10.—Cortex, rabbit, dura intact. Three days after exposure. The perivascular and perineuronal spaces are smaller than after the dura is removed (compare with Figure 9). Hematoxylin and eosin stain; magnification × 625.

neuronal spaces, following in time the appearance of perivascular fluid. These findings show that exposure of the brain eventually produces a condition indistinguishable from that described for cerebral edema. Functional vascular disturbances in the form of congestion, stasis, and dilation of the capillaries and veins were also present in these tissues.

There appears to be general agreement that trauma to the brain results primarily in vascular disturbances which secondarily produce brain swelling and edema. However, there is no unanimity regarding the precise nature of the circulatory changes causing these conditions. A number of investigators have observed vascular pathology similar to that described above. Evans and Scheinker[3] postulate that trauma causes vasoparalysis of capillaries and venules, leading to a slowing of the blood stream. They also postulate that the local accumulation of CO_2 leads to a further dilation and increased permeability of the vessel wall. As a consequence, the parenchymal changes associated with cerebral swelling and edema would occur. A similar view is held by Prados et al.[4,5] on the basis of their experiments on the reaction of the brain to air exposure. These workers noted dilation of the cerebral vessels and congestion of blood. They hold that the resulting ischemia causes the parenchymal changes. In addition, on the basis of their experiments with trypan blue, they found evidence of an increase in the permeability of the blood-brain barrier. White, Brooks, Goldthwait, and Adams,[10] in studying brain swelling after experimental concussion, did not observe any differences in the vessels between animals with brain concussion and those which were not traumatized. According to these investigators, the swelling is caused by extravasation of fluid through the capillary walls and is not due to the escape of red cells, vascular congestion, or distention of the ventricles as a result of increased amounts of fluid.

Reid,[11] studying cerebral edema occurring around intracranial tumors, found an increase in the number of blood vessels and proliferation of their endothelial cells, but did not report on any vascular pathology in relation to cerebral edema. Greenfield[12] attributes cerebral edema associated with intracranial tumors to cerebral anoxia. He further suggests that venous obstruction and reduction in size of the capillary bed may play some role. In most cases he found no morphological changes in the blood vessels. Obrador and Pi-Suñer[2] studied through cranial windows the swelling of the brain following the production of lesions of the floor of the fourth ventricle and medulla. They believe that the swelling of the brain under these conditions has a vascular origin and is the result of generalized vasomotor disturbances. They noted a dilation of the perivascular spaces but did not observe any other histologic changes in either the vessels or the parenchyma. In agreement with Apfelbach[6] and with Bonvallet and Le Beau,[7] they failed to observe trypan blue permeability of the brain with acute swelling due to a lesion of the brain.

The present observations indicate that cerebral edema is accompanied by histologically observable vascular changes and, in addition, by changes in the blood-brain barrier. The two may be related in that the ischemia resulting from the circulatory deficiencies may damage the endothelium and thus cause an increase in the permeability of the blood-brain barrier.

Apfelbach,[6] Bonvallet and Le Beau,[7] and Obrador and Pi-Suñer[2] found that cerebral edema may occur without an increased permeability for trypan blue. This may indicate that an increase in the permeability of the vascular endothelium for fluid, resulting in edema, does not necessarily involve an increase in the permeability of the blood-brain barrier per se. It should be stressed, however, that trypan blue is not a sensitive indicator for changes in the blood-brain barrier, since detection of its presence is largely limited to macroscopic observation,

in contrast to the aminoacridines, which, because of their fluorescence, can be detected in great dilutions and at a cellular level. On the basis of the present experiments, it appears that the occurrence of cerebral edema is generally accompanied by an increase in the permeability of the blood-brain barrier.

The in vivo staining of the nervous tissue surrounding the meningioma incidentally occurring in one animal which was kept alive for seven days after exposure of the brain was stronger than in nervous tissue of the exposed area further removed from the tumor. From this, it may be concluded that the tumor affected the permeability of the blood-brain barrier of the surrounding nervous tissue. This change in permeability is probably independent of the permeability changes in the blood-brain barrier resulting from the exposure of the brain.

It is of interest to note that a relatively mild trauma to the brain, such as an exposure for 45 minutes, can cause such drastic changes in the permeability of the blood-brain barrier. However, it is obvious that the permeability changes in these experiments are not permanent. The reversibility of the cerebral edema is accompanied by a restoration of the blood-brain barrier to relative impermeability. This further strengthens the hypothesis that there is a causal relationship between cerebral edema and changes in the permeability of the blood-brain barrier.

Summary

The changes in the permeability of the blood-brain barrier occurring during cerebral swelling and edema were examined by using aminoacridine dyes. Cerebral edema was experimentally produced by trephining and exposing the brain for 45 minutes. In one series of animals the dura was removed, and in another the dura was left intact.

On the basis of observations with these dyes on the in vivo staining of the vascular endothelium, as well as of the parenchymal cells, it can be shown that there is a increase in the permeability of the blood-brain barrier during cerebral edema produced by exposure of the brain. The increase in permeability is reversible. It reaches a maximum in three days and is then gradually restored to its normal permeability. The cerebral edema, as well as the increase in the permeability of the blood-brain barrier, is less severe when the dura is left intact.

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Effect of High-Intensity Focused Ultrasound on Nerve Cells in Spinal Cord of Mouse

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Introduction

Previous work reported on the histopathology of high-intensity focused ultrasound on the central nervous system of experimental animals has been carried out at a frequency of 980 kc. using a multibeam transducer,[1-3] or at 835 kc. using a focused beam.[4] The present communication deals with the minute structural changes in the spinal cords of mice irradiated at a frequency of 2.5 mc. with a focused beam. Details of the method and dosage have already been reported.[5]

Material and Methods

Adult white mice were irradiated through the intact shaved skin through the prominent hump in the dorsal spine. This lies approximately at the level of the eighth thoracic vertebra. The transducer cone was filled with degassed isotonic saline and covered with goldbeater's skin; this allows the saline solution to permeate slowly and so ensures a liquid contact between the transducer and the experimental animal through which the sound waves may pass. Ultrasound was delivered as a pulsed dose at the following parameters: 2.5 megacycles per second with a voltage across the quartz crystal of 800. This was given as five pulses of 0.4 second, with an interval of 0.6 second between pulses. The mice were killed in pairs at 1.0, 2.0, 4.0, 8.0, and 24.0 hours after irradiation, having been injected subcutaneously half an hour before being killed with 0.25 cc. of trypan blue.* Two additional animals were allowed to survive for 30 days but were not injected with trypan blue in vivo.

Immediately after the animal was killed, the entire vertebral column was cut out and, after removal of two or three laminae, was placed in 10% formalin. Two weeks later all the laminae were removed with a pick and the cord and membranes dissected free. In the case of the 30-day mice, however, the bone was decalcified in edathamil (Versene)† at a pH of 9. The segments of cord containing the lesion were embedded in paraffin and cut at 15μ. They were stained by the Nissl technique, using methylene blue as the basic dye.

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Department of Anatomy, the University of Liverpool.

* This procedure was suggested by Dr. Louis Rakay.

TABLE 1.—*Clinical States After Irradiation*

Paraplegia	3
Left monoplegia	5
Left monoparesis	2
Total	10

Results

As the mice had not been anesthetized for the procedure, the clinical states were assessed immediately after irradiation. The results are presented in Tables 1 and 2.

TABLE 2.—*Clinical States and Survival Times*

Mouse No.	Clinical State	Survival Time, Hr.
3B	Left monoparesis	1
4A	Paraplegic	1
2A	Left monoparesis	2
5A	Left monoplegia	2
5B	Left monoplegia	4
6A	Left monoplegia	4
1A	Paraplegic	8
1B	Paraplegic	8
4B	Left monoplegia	24
6B	Left monoplegia	24

In order to correlate the figures in Table 1 with the survival time and the changes to be described, the clinical findings may be retabulated in Table 2.

It should be added here that two mice in this series, irradiated at these standard parameters, were rendered "weak" only and were discarded. Their significance will be discussed later.

† Supplied by the Bersworth Chemical Co., Framingham, Mass.

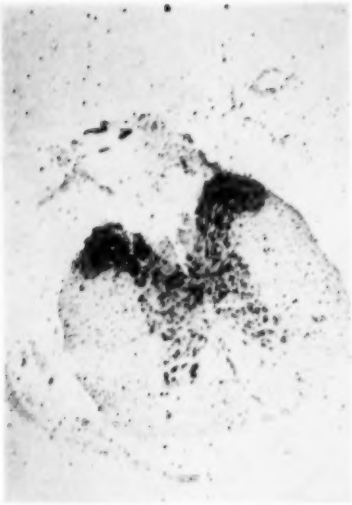
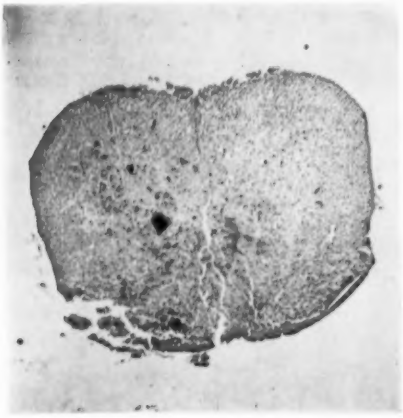


Fig. 1.—Normal thoracic cord of mouse. Nissl stain.

On laminectomy, the areas of the cords which had been maximally irradiated were found to be stained with trypan blue, as seen with all membranes intact; these regions were also macroscopically hyperemic. On removal, many of the cords were found to be extremely friable, so that they tore when cut with the microtome; they were also compressed dorsoventrally (Figs. 2 and 3).

Microscopic examination showed a great decrease in cell population even at one hour

Fig. 3.—Thoracic cord eight hours after irradiation. Nissl stain.



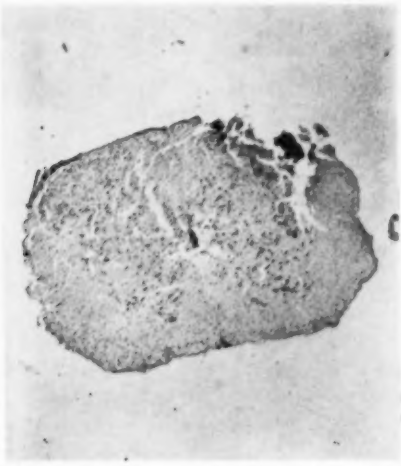
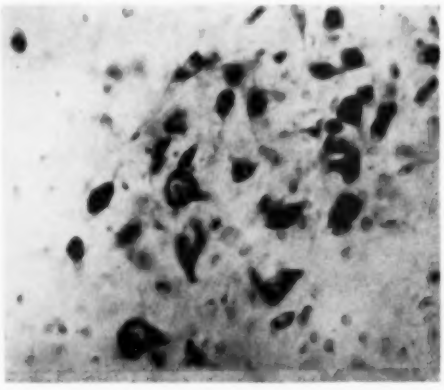


Fig. 2.—Thoracic cord one hour after irradiation. Nissl stain.

(Fig. 2). Figure 1 shows a normal Nissl-stained mouse thoracic cord for comparison. It will also be noted from Figure 2 that there is slight hemorrhage in one dorsal horn and some slight indication that depopulation is greater in the ventral than in the dorsal horn. The ependyma surrounding the central canal can also be seen to be intact.

At two hours, in an extremely friable cord, cell depopulation has progressed further. At four hours it has proceeded further, and at eight hours (Fig. 3) it is seen to have progressed even further. The cells are less hyperchromic than in Figure 2,

Fig. 4.—Normal ventral horn cells in mouse spinal cord. Nissl stain; ×370.



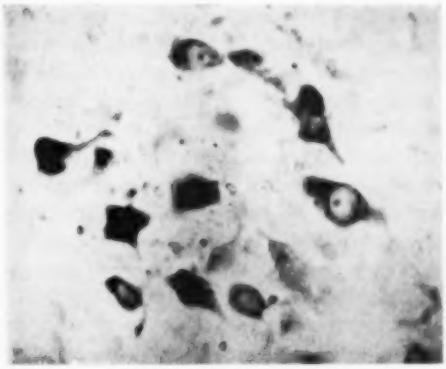


Fig. 5.—Ventral horn cells one hour after irradiation (from same section as Figure 2). Nissl stain; reduced to 76% of mag. × 370.

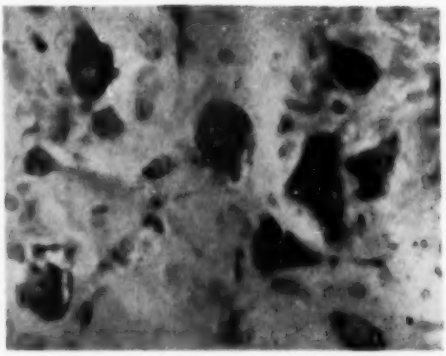


Fig. 6.—Ventral horn cells two hours after irradiation. Nissl stain; reduced to 76% of mag. × 370.

indicating that chromatolysis is more advanced. At 24 hours, however, the cell population appears to have suffered no further reduction.

Owing to the friability of the cords, it cannot clearly be decided whether the irregular cavities in the matrix are due to the action of the ultrasound or are an artifact due to cutting. However, Figures 2 and 3 do demonstrate a pericellular space, especially around the ventral horn cells.

Examination of the surviving cells showed the greatest amount of change in the ventral horn cells; indeed, the surviving posterior horn cells showed no change in the vast majority of cases. Figure 4 shows normal mouse ventral horn cells for comparison. Figure 5 (from the same section as Figure 2) shows ventral horn cells one hour after irradiation. Three of these cells are seen to be uniformly stained and hyperchromic. Others show loss or blurring of the nucleolus and vacuolation of the cytoplasm. Two are reduced to ghosts. There is one comparatively normal cell. Pericellular spaces can be observed. The cells can also be seen to be enlarged.

At two hours (Fig. 6), the vacuolation of the cytoplasm is more evident, and pyknosis is occurring in some nuclei. Figure 7 (from the same section as Figure 3) shows the appearance of ventral horn cells eight hours after irradiation. The vacuoles are

Fig. 7.—Ventral horn cells eight hours after irradiation (from same section as Figure 3). Nissl stain; reduced to 86% of mag. × 370.

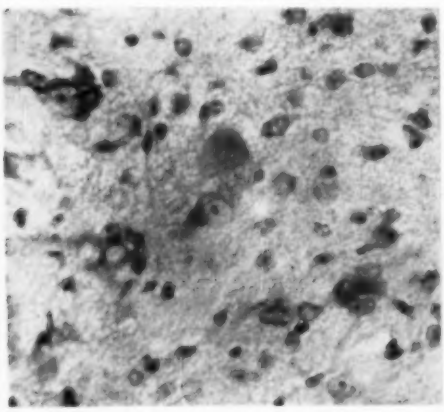
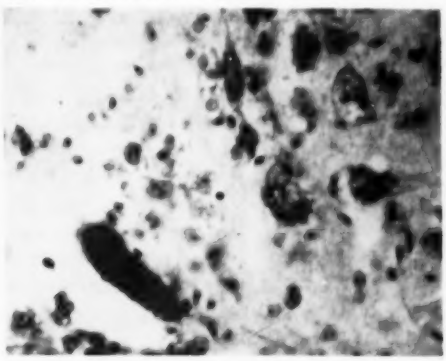


Fig. 8.—Ventral horn cells and central canal 24 hours after irradiation. Nissl stain; reduced to 76% of mag. × 370.



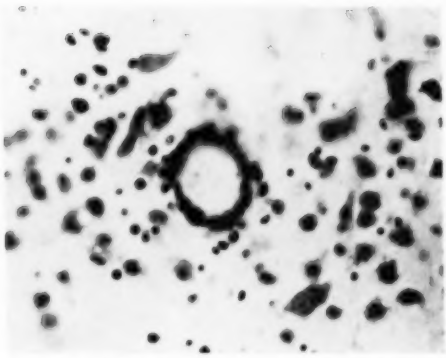


Fig. 9.—Ventral horn cells and central canal 30 days after irradiation. Nissl stain; reduced to 76% of mag. ×370.

larger than in Figure 6, and the degenerative process is generally more advanced. At 24 hours (Fig. 8), vacuolation is extreme, and it can be seen that in some of these cells the membrane is intact; the ependyma is normal. That this vacuolation per se is not necessarily fatal to the nerve cells is shown by the 30-day cord (Fig. 9). Vacuolation is still evident in many cells, which have returned to normal size, and a glial reaction is evident.

In all cases the meninges, ependyma, and dorsal root ganglion cells were normal. As far as could be seen with this staining technique, the nuclei of the glial cells were normal in appearance, and so were the vast majority of blood vessels.

Comment

The dose of ultrasonic radiation used was chosen because it had been found by trial and error to be the minimal paralyzing dose. That the effect is extremely variable is shown by the fact that the clinical response varied from "weakness" to complete paraplegia, though monoplegia or monoparesis was the most frequent result. It is evident therefore, at these parameters, that cell damage is out of all proportion to fiber-tract damage. Even in cases with monoparesis (Fig. 2) there is little evidence of lateralization of cell destruction. This is in contradistinction to the findings of Fry and his co-workers,[2,3,6] who state that ultrasound damage "suggests a specificity for nerve fibers over nerve cells." However, they were working at a frequency of just under 1 megacycle per second, while the current report is concerned with damage produced at a frequency of 2.5 megacycles per second. It may be, then, that this higher frequency exerts a specifically greater destructive effect on nerve cells than on nerve fibers. In common with other workers, it is found that damage to blood vessels is extremely slight.[1-4] Bakay's suggestion of injecting trypan blue before killing the animal, but after irradiation, shows that capillary permeability is altered; indeed, as the sections showed a blue tinge before Nissl treatment, it must be concluded that in the area of the lesion the "blood-brain barrier" had been broken down. Bakay[7] had previously demonstrated this to be the case in lesions made at a depth in the cat brain. Lehmann[8] had also noted edema in mouse tails, which he attributed to altered capillary permeability.

The greater susceptibility of ventral horn cells than of cells of the posterior horn had previously been mentioned by Wall et al.,[1] but the particular type of damage observed in these mouse cells was so remarkable that other possibilities had to be considered. The first of these possible factors was heat, especially in view of the fact that laminectomy had not been performed prior to irradiation. Fry, Wulff, Tucker, and Fry[9] have shown that at a frequency of 980 kc. per second with continuous wave the temperature rise in spinal cord is 1.8 C per second, whereas in bone it is 55 C per second. It was therefore decided to investigate heart paralysis in mice. For this purpose, mice were placed in a hot room with a dry-bulb temperature of 104 F for six to eight hours, after which time they became quadriplegic and died.‡ Examination of the cord indeed showed vacuolation of ventral horn cell cytoplasm, but of quite

‡ This procedure was carried out by Mr. G. A. Harrison.

different type from that herein described. The cytoplasm had merely drawn away from the cell wall, remaining attached by a few strands; the appearance was that of an irregular star in a ring, exactly similar to that of cells treated in hypertonic saline. Moreover, other cellular elements were similarly damaged.

As the animals had not been perfused per artery at death, fixation artifact had also to be considered. Mouse spinal columns were removed and left for periods up to 24 hours before immersion in 10% formalin. On examination, little or no change was observed in the nerve cells, save that in a few scattered cells the appearance of the hypochromic phase of chromatolysis could be observed.

In fact, strongly militating against artifact was the observation that ependyma, meninges, and dorsal root ganglion cells in the irradiated areas were normal. Moreover, a few normal ventral horn cells and many normal dorsal horn cells were seen in every section.

The type of change seen in the motor horn cells has not been described in any other animal. As pointed out by Wall et al.[1] and Barnard et al.,[3] there is a process of destruction by chromatolysis that is remarkable only by the rapidity with which it takes place, but in the case of the mouse this is accompanied by vacuolation. Wall et al.[1] have described some vacuolation in cells whose limiting membranes have been disrupted, but none in intact cells. Fry [10] states that the process is not one of physical disruption of cellular or nuclear membranes, and Hueter, Ballantine, and Cotter [5] speak of "rupture and restitution of molecular bonds." Is a process of physical cavitation being observed? Schmitt and Uhlemeyer [11] have shown that physical cavitation may occur in the ultasonic disruption of unicellular organisms, but Harvey [12] has demonstrated that disruption of such organisms can occur without cavitation. Barnard et al.[3] state that no histological changes can be seen in the cat brain for five to eight minutes after irradiation, but their specimens, irradiated at 1 megacycle, did not show vacuolation. Against this being a true process of cavitation is the fact that the size of the vacuoles seems to increase with time (Figs. 5-9).

This leads to the question as to whether the vacuolated cells have been damaged at the time of irradiation but are not killed by the process (Fig. 9), or whether they are undamaged at the time of irradiation but subsequently become so. In the latter contingency, there must be postulated the liberation of a toxin which remains confined to the cord and which is able to exert its destructive effect after prolonged periods of time. Wall et al.[1] have shown that chromatolytic cells, in the earlier stages of destruction, can be found up to at least two weeks after irradiation. Fry [10] has shown that in peripheral nerve fibers it is possible to produce a reversible change, as shown by recovery of ability to conduct impulses, while Cotter [13] has observed partial clinical recovery in mice paralyzed by ultrasound. No workers have observed histological changes in animals killed immediately after irradiation.[1,3,10] In the present series of experiments, no significant decrease in cell population was observed after eight hours. It is therefore concluded that damage probably occurs primarily at molecular level during irradiation,[5] but that this progresses for at least eight hours in mice. After this period vacuoles made by the breakdown of cytoplasmic molecules may increase in size, but, that, in the absence of nuclear damage, is not necessarily incompatible with the viability of the cell. The possibility of physical cavitation cannot, however, be excluded at this frequency; Fry's [10] observation that less damage occurs when animals are irradiated under increased atmospheric pressure tends to support this hypothesis.

Summary

Mice were irradiated with a minimal paralyzing dose of pulsed focused ultrasound at a frequency of 2.5 megacycles per second.

Damage to nerve cells in the area of irradiation was greater than that to nerve fibers.

The cells of the ventral horn were more susceptible than those of the dorsal horn.

Vacuolation, as well as chromatolysis, was observed. Apparently, not all vacuolated cells were chromatolytic or vice versa.

In the absence of chromatolysis, vacuolation is not apparently incompatible with the continued life of the cell.

The irradiations were carried out in the laboratory of the Medical Acoustics Research Group at the Massachusetts General Hospital. Drs. H. T. Ballantine and T. F. Hueter gave advice and encouragement, and the Misses Betty Francis and Jane Rosenthal, technical assistance. Mrs. Cynthia Morley prepared the slides.

This work was made possible in England by a grant from the Medical Research Council, and in the United States by a grant from the Department of the Army.

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News and Comment

SOCIETY NEWS

Houston Neurological Society.—The Houston Neurological Society, Houston, Texas, announces a symposium on "Pathogenesis and Treatment of Parkinsonism" to be held on March 13, 1958, as part of its Sixth Annual Scientific Session. Participants will include Dr. Malcolm Carpenter, New York; Dr. Harry Kaplan, Brooklyn; Dr. Arthur Ward, Seattle; Dr. Robert Schwab, Boston; Dr. Russell Meyers, Iowa City; Dr. Paul Bucy, Chicago; Dr. Irving Cooper, New York, and Dr. A. Earl Walker, Baltimore.

The American Neurological Association.—At the 82d Annual Meeting of the American Neurological Association, held in Atlantic City, N. J., on June 17-19, 1957, the following officers were elected for the coming year:

President, Israel S. Wechsler; president-elect, Bernard J. Alpers; 1st vice-president, Russell N. DeJong; 2d vice-president, Bronson S. Ray; secretary-treasurer, Charles Rupp; assistant secretary, William F. Caveness.

The 83d Annual Meeting of the Association will be held at the Claridge Hotel, Atlantic City, June 16-18, 1958.

ANNOUNCEMENTS

Congress of Neurological Surgeons.—The Congress of Neurological Surgeons will hold its Seventh Annual Meeting at the Statler Hotel in Washington, D. C., Nov. 7, 8, and 9, 1957. The program will be devoted to a consideration of various aspects of pediatric neurosurgery. Dr. Francis C. Grant will be the principal guest speaker.

Inquiries should be directed to Dr. Philip D. Gordy, Suite B-1, Professional Building, Augustine Cut-Off, Wilmington, Del.

Books

BOOK REVIEWS

Systématique et électroencéphalographie des encéphalites et encéphalopathies. By J. Radermecker. Price 2.800 fr. Pp. 244. Masson & Cie, 120 boulevard Saint-Germain, Paris, 6e, 1956.

This study is based on material from the Bunge Institute and the Antwerp Institute of Tropical Medicine and includes children and adults whose diseases were either European or African in origin. The author discusses sixteen varieties of acute viral meningitis and meningoencephalitis; two types of subacute and chronic meningoencephalitis, and suppurative meningitis; some fourteen types of primary encephalitis, and many types of postinfectious and toxic encephalitis. A few lines of description of each disease are given. In some cases photographs of brain slabs or low-power photomicrographs illustrate the sketch. In others a very brief case history and microscopically reproduced electroencephalograms (one-sixth natural size) are provided. Of the seventy-eight figures, thirty-six are electroencephalograms. The literature bearing on each disease is discussed. A twenty-one-page bibliography concludes the work.

The author sought to determine (1) whether the comparison of electrical disorders observed in encephalitic processes of different topography in the nervous system would clarify the meaning of the various electroencephalographic elements observed in these and other neurological disorders (it did not), and (2) whether serial electroencephalograms could help in the differential diagnosis of primary encephalitides and postinfectious encephalopathies (they did not). The author notes that serial electroencephalograms continued after clinical recovery from encephalitis may foretell the appearance of postencephalitic seizure disorders.

Fear of Electroconvulsive Therapy

Notes from a Patient's Diary

MERTON H. FRIEDMAN, Ph.D., Boston

It is the purpose of this paper to indicate the nature of the fear of electroconvulsive therapy (ECT) expressed by a patient who kept a diary while undergoing such treatment. Heretofore, a personal document of this nature has not been available in the literature for study.

Previous studies concerned with the reactions of patients to ECT, other than the purely theoretical, have dealt with (1) observations of manifest fear[2,3,11,20]; (2) survey interviews before and after treatment[10,13]; (3) material elicited during a course of psychotherapy which followed ECT,[15] and (4) in one instance,[4] material written as a term paper sometime after treatment by a student who reminisced of his experiences as a patient. The uniqueness of the document to be presented here lies in the fact that it illuminates the day-by-day reactions to ECT of a very literate patient—reactions which were recorded while the emotional impressions of the treatment experience were still vivid in the writer's mind.

Submitted for publication April 19, 1957.

From Psychology Section, Psychiatry and Neurology Service, Veterans' Administration Hospital.

This paper was presented in part at the regular meeting of the Boston Society of Psychiatry and Neurology, Jan. 17, 1957.

Dr. Eugene J. Balcanoff, Staff Psychiatrist, Veterans' Administration Hospital, Boston, made many helpful comments during the preparation of this paper.

Having behind us the accumulated experience of almost two decades of ECT and the now commonplace observations of fear in many patients undergoing such treatment, it may seem surprising to suggest that at one time there was serious doubt as to the presence of such a reaction. Indeed, Cerletti and Bini,[7] who, in 1938, first advocated the use of electrically induced seizures as a method of treatment for the mentally ill, were impressed by the absence of the fear reaction so prevalent in patients undergoing the then widely used pentylenetetrazol U. S. P. (Metrazol) therapy. It was emphasized that one of the prime advantages of the new method was the total unconsciousness of the patient during the evolution of the treatment: "These patients, asked about their sensations, affirm that they know nothing, simply of having slept." * In the years immediately following the inception of ETC, other writers[9,17] were similarly impressed with the minimal presence or total absence of fear in patients undergoing the treatment.

However, as early as 1940 there appeared in the literature serious doubts as to the absence of fear, the authors actually suggesting the possible therapeutic properties of such fear. Abse,[1,3] in England, was

* Cerletti and Bini,[7] p. 267. A translation of this article, originally published in Italian, was provided by Dr. Pietro V. Marchetti, Department of Psychology, University of Illinois.

among the first to stress the traumatic, fear-producing properties of ECT.

> The patient is being exposed to repeated danger situations, and unless he has become quite demented and introverted, he reacts by fear of this threatening external danger. . . . Even in the absence of verbal formulation [in the writer's experience, *non est*], the patient's behaviour clearly shows during the treatment his desire to evade the repetition of the anxiety experience. The behaviourist and sensationist would hardly discount the predominance of anxiety after observation of the pupils, pulse, respiration and perspiration, etc. In short, we can not avoid the observation of fear.[24]

Similar observations have been reported in the American literature in succeeding years.[8,10,12,18-20,23]

In light of the previously enumerated observations of fear, it is interesting to note that in 1950 Cerletti [6] took cognizance of the emotional reactions of his patients. Whereas in his original report, some 12 years earlier, he makes no mention of the presence of fear in his patients receiving the then new treatment, he later writes of the readily demonstrable affective correlates of the therapy: ". . . the patient's fear of therapy which leads some to want to stop it." [25]

When they were asked why they wished to stop the treatment, Cerletti's patients were unable to answer specifically other than to say that they were afraid. Of what they were afraid they could not tell, but yet they were manifestly fearful of the treatment. Cerletti concludes, therefore:

> There must be a vague recollection—organic memory—of the first "terror-defense" reaction. I believe that name "terror-defense" expresses the biological significance of epileptic fits. The terror phase, although taking place during unconsciousness, leaves specific biochemical and psychological changes in the organism that later emerge generically into the conscious sphere.[26]

Similarly, Hayward [15] recently reported a verbatim interview with a female patient who had undergone 34 electroconvulsive treatments. This patient clearly verbalized what she felt as "real terror."

In an attempt to provide additional credence to the many observations of fear in patients undergoing ECT and to delineate the nature of this reaction, there follow portions of a written diary kept by a patient who, at the time, was undergoing a course of ECT at a Veterans' Administration Hospital. It will be seen that the fear reaction manifested while the patient was under this treatment assumed a prominent role in his thinking.

Brief History of Patient

The author of the diary is a 34-year-old, white, unmarried graduate student who was admitted to the closed-ward section of the Veterans' Administration Hospital in the spring of 1951 because of increasing overactivity and bizarre behavior, manifested by grandiose delusions and hallucinations. The diagnosis on admission was that of a schizophrenic reaction, undifferentiated type.

The patient's first reported psychotic experience, in which he wanted to destroy the present world civilization, occurred after one of his professors allegedly made a homosexual advance toward him. His reaction to this alternated between panic and manic elation. Although the psychotic episode subsided within 24 hours, and the patient continued his graduate studies, he threw himself into a great deal of heterosexual activity with a girl friend, who soon became his mistress. While in church on Easter Sunday, 1951, he felt that marriage to his mistress was the only solution to his problems. When advised to go slowly by a psychiatrist, with whom he had been in therapy for over a year, he became increasingly overactive and bizarre. Following this he had his first hallucination, in which he saw a mystic rose in the genitals of his mistress. It was shortly thereafter that he was hospitalized.

On admission the patient was confused about his identity and was repeating his name over and over again, like an incantation. At times he was overactive and bizarre, and at other times he was mute and inaccessible. The physical examination, laboratory findings, and x-ray studies were all within normal limits. Repeated chest plates showed evidence of an old tuberculous infection.

In the hospital the patient was given intensive psychotherapy; despite this, his bizarreness and inaccessibility increased, leading to a course of 60 insulin comas. He improved for a short while, but in the early part of 1952 he again became bizarre and overactive. He was given a course of 12 electroconvulsive treatments in June, 1952; but when his bizarre overactivity returned, within a month after termination of ECT, he was given a second course, of 15 treatments. He quieted down sufficiently so that intensive psychotherapy was carried on by a resident psychiatrist until July, 1953, when he was treated by a staff physician for two and a half years. It was during this last

period that the diary to be discussed below was given to the psychiatrist by the patient. Prior to this presentation, the psychiatrist was unaware of the existence of such a personal document.

Diary

This document actually covers the period from Sept. 2 to Sept. 29, 1952; but limitations of space preclude its total inclusion. Only selections from the entries for the period Sept. 2 to Sept. 26 are cited. Where entries are enclosed by parentheses, material has been summarized for the sake of brevity. Letters of the alphabet are used to replace the names of staff, ward personnel, and patients referred to in the diary.

"Sept. 2, 1952: (Discussion of ward events and thoughts about marriage) Fear of ECT. (Further comments about relationship to girl friend) Dr. also said that I would be getting ECT tomorrow and Monday, since it seemed to be having 'such good results.' (Comments about work in occupational therapy; his hopes for eventual discharge from the hospital)

"Sept. 3: 0530 awakened early (in darkness) by C; slipped thermometer, thus begins 'ritual of getting ECT blast.' Attendant comes around to tell me I should 'get my clothes.' I think back over group life of past few years—specially of France. W next to me lets out a long fart. Two hours to go to receiving electroshock. Much better to get it while sleepy but 'build-up' makes relaxing virtually impossible. Lights are turned on all over dormitory. Sixteen patients are stirring, making noise. Study effects of 0530-0730 build-up in contrast with blast administered to person just awakened in private room. Special study of operation-room ritual on the patient—formal white clothing, etc. (Brief reference to possibility of using these observations for course paper when he returns to his graduate studies)

"I go across the hall, get clothing, put it on, and return to dormitory with time, time, time, and no breakfast until after blast. Memories of (school) life flood back. Vast status effect in being on treatment.

"'Chow.' A (attendant) goes over, pokes B, and announces chow. V gets up singing. H reads from the Scripture, 'And He says man was made for the Sabbath and the Sabbath was not made for man.' Man opposite gets up, tells me, 'Let's go, boy; chow!' Then W next to me gets up, dresses, and goes in to breakfast; likewise B. L comes back to check his bedside table, adjusts a towel daintily. Then I am alone. After, L comes over, asks if I'm going to eat. I say, 'No, I'm going to have a treatment.' He acts embarrassed, says, 'Take it easy,' and leaves. H comes in from breakfast and paces up and down. L comes in again to arrange his towel, stops again as he goes by, says, 'Take it easy,' and goes out. Then C wanders in and out; then one can hear E 'whooping,' but he does not come into the dormitory. I have another cigarette and think of how well my mind is working and wonder what this ritual all adds up to. It seems bad to have no 'company' while waiting. Last call for chow by attendant—asks T who wants to sleep. T remains in bed. H paces up and down in front of foggy windows. I wait and write. It is obscene now, for I am wide-awake and clear-headed. P returns from breakfast. Crickets and streetcars running outside. C strides in from breakfast and stands at our windows for a while.

"Other patients return from breakfast. V goes in and out several times. I realize how much I miss breakfast and think how I enjoyed it yesterday and Wednesday. I think of J (girl friend) and why I am not at (university); then I think of my family and, finally, of my own helplessness. W wanders in and out. V wanders in and out, 'maneuvering' against imaginary gladiatorial foes. Sounds of a cricket outside the window—and of streetcars and trucks. I wait, I want to get it over with. I think of J and like to think of being with her in (city). Why am I still in this hospital? I cough and spit and wait. Finally, I light another cigarette and wish for chloroform or some escape, and time is like a pit, and H says I should be smoking long cigarettes like O. Time, time, time, he says, is all we have to worry about—evil deeds carry their own reward.

"The sound of a nurse's laughter comes from the hall. I 'prepare myself.' The short attendant comes in and empties the wastebasket; says, 'How are you this morning? Pretty good. Good.' (The next to the last turn of the screw) No company. My time arrives—I go up to (ward where treatment is administered) with (attendant). As I go into chamber, S is carried out unconscious. It is his last 'shock.' Take me next, about 0900; I come to about 0915, feel peaceful, at first do not remember 'shock.' Have some breakfast, then go to (another ward). (Three patients) and I have breakfast together on (ward). Then I go down with E and attendant to (another ward). Two things, no, three, to ask (treating physician): (1) when shocks will end; (2) when weekend pass; (3) when discharge—preferably by Christmas.

"No answers from (physician), except that schedule of two a week is a good sign. Letter arrives from J (girl friend), referring to last visit. Question arises as to what 'shock' does to the memory? Difficulty in answering letters

(Brief reference to relationship with girl friend, planned trip to football game)"

Subsequent references to ECT in the diary:

"Sept. 6: Relatively relaxed ECT this morning. . . . (Physician) stops by to tell me that there will be only three more ECT's. Wasn't it easier to relax with him this morning?

"Sept. 9: I see Dr. W (another physician giving ECT) in the office and, probably because of my remaining shocks, feel uncomfortable.

"Sept. 10: ECT on (ward), then breakfast and busy day.

"Sept. 15: Wednesday ECT on (ward)—next to last one—a 'dazzling one.'

"Sept. 19: Associate ECT or stimulus-response of ECT—good moral equivalencing?

"Sept. 21: I find my mind 'jams up'—yet certain events, even rather 'obscene,' rise relatively clearly—relation to (1) ECT; (2) long-term personality conflicts; (3) short-term personality conflicts; (4) interaction difficulties.

"Tomorrow morning my 'last shock'—then what? (Reminisces of hospital experiences) Doctor's announcement of ECT to be had and my escape† from the library (of hospital), cab to (city), cashed check, then to buy suit and arrest—jail—back to hospital and ECT and memories flood back of room and phantasies—of being cinnamon brown bear, elected vice-president, etc. Later terror of ECT—fascination and why fascination of humiliation—of lack of communication, etc.?

"Sept. 22: Wednesday. Slept until moment for ECT—much easier that way—no build-up of tension. I relaxed on treatment table, had a little chat with (physician) before treatment; and there ensued a dazzling 'flash,' from head down through body.

"Sept. 24: H asks about ECT. 'Did you have one this morning?' For third time I told him I was through. Doctor came by at suppertime—we talked probably for an hour. He noted the end of ECT treatment, congratulated me.

"Sept. 26: One reason ECT hits one so hard is that it dramatizes the classification 'psychotic.'"

Analysis of the Diary

The contents of this patient's diary leave no doubt as to the presence of a very real fear of ECT. For this patient, at least, the question is thus not one of whether the treatment was anxiety-arousing but rather: What was it about the treatment that was so fearful? It is possible to isolate the expression of four major fears which served to make the treatment a noxious experience for him: (1) fear of punishment; (2) fear of his helplessness; (3) fear of humiliation, and (4) fear of what the treatment would do to his mind.

Fear of Punishment.—References to "blast," "evil deeds" carrying their own reward, "last turn of the screw," "moral equivalencing," "tension," the wish for chloroform and escape, all suggest the interpretation of treatment as punitive.

The receiving of treatment as retribution by patients, based upon a need for atonement for sins, has been a widely offered psychogenic interpretation of the underlying mechanism of ECT. The major impetus for such theorizing seems to have stemmed from work with depressed patients and their marked and immediate response to ECT.[5,21] However, the possibly punishing aspects of the treatment have been suggested by Gordon[14] as one of the major psychodynamic mechanisms inherent in all convulsive therapies. Abse[3] pictures the physician repeatedly subjecting the patient to a traumatic situation, which becomes equated with punishment.‡

Fear of Helplessness.—References made in the diary to the "operation ritual," and to feelings of loneliness and being subjected to a "build-up," suggest the patient's helplessness in the face of the little-understood treatment he was about to receive. Indeed, it is just such a feeling of impotence that the patient consciously emphasizes when he writes, "I think . . . finally of my own helplessness."

Since the treatment is administered by a source external to the patient receiving it, and thus not subject to his control, emphasis has been given by some to the manifest dependency of the patient upon the physician. Gordon[26] describes the patient as "helpless and dependent" (who "sees in the physician a mother"). Abse[2] and Mosse[19]

† The patient eloped from the hospital after the third treatment of his second course of ECT. He went to a nearby city, where he was subsequently apprehended and returned.

‡ See also Mosse[19] and Wilson.[28]

emphasize the similarity of the patient to a child dependent upon the good will of a psychiatric parent and authoritative figure.

Fear of Humiliation.—The discomfort this patient felt in the presence of physicians associated with ECT and the embarrassment he attributes to another patient whom he has informed of his own impending treatment suggest the presence of a sense of personal humiliation. Indeed, the emphasis given in the diary to the "vast status effect" of treatment; the "effects of beginning treatment in a new hospital, where most patients are not on treatment"; the "fascination of humiliation"; the feeling that the treatment "dramatizes the classification 'psychotic'"; his apparent defensive irritation with a patient whom he had to tell three times that he was "through" with treatment—all suggest that lowered self-esteem was an important contributory factor to the patient's fear of ECT. In this connection, Hayward's [15] patient also describes the experience as "humiliating." Fisher, Fisher, and Hilkevitch [10] briefly note a similar reaction occurring during the course of interviewing a number of patients undergoing ECT.

Fear of Damage to His Mind.—Several references are made by the patient in his diary to the functioning of his mind. Although given in a characteristically intellectualized manner (i. e., "Question arises as to what 'shock' does to the memory"), there still appears to be a real concern over what the treatment might do to his mind ("My mind jams up").

Kalinowsky [16] indicates that some patients show an unpleasant reaction to both the memory difficulties and the organic character changes following treatment which frighten them. Similarly, Frosch and Impastato [12] mention the general and specific psychological reactions to a treatment which involves a "drastic physical assault" and produces organic brain alterations.§

§ See also Tanner.[23]

Comment

The preceding discussion indicates that much of the fear of treatment expressed by the patient in his diary has a valid community with previous observation and theory. At the same time, however, two aspects of these emotional reactions stand out as being quite different from the results of previous studies. First, one of the fears expressed by this patient, that of humiliation, has not been explicitly delineated in the literature beyond the sexual connotations it assumed for Hayward's patient [15] and a brief reference to its presence in a survey report by Fisher, Fisher, and Hilkevitch.[10] Second, while other patients have expressed one or another of the remaining three fears, such expression has not included the same number, or assumed the same form and content, as appears in this particular instance. These two observations thus suggest the idiosyncratic nature not only of the reaction of this particular patient to the treatment stimulus but also that of any other patient. These observations also support the hypothesis advanced by Abse [3] that the meaning of reactions to ECT can best be approached through an analysis of their unconscious determinants.

Although Abse [3] emphasized the primarily negative reactions to ECT, by idiosyncratic it is here meant that the emotional response to such treatment—be it fearful or resigned or even complacent—may be considered as reflecting a particular type of defensive attempt to cope with a traumatic experience. Implicit in such reasoning is the expectation that fully understanding a patient's reactions to ECT may provide significant insight into the dynamics of his illness. Concomitantly, by understanding the dynamics of a patient's illness, it may be possible to predict the nature of his reactions to the treatment and, in so doing, comprehend the symbolic meaning of these reactions.

It is recognized that the approach suggested here differs from various monistic hypotheses, such as the recent attempt by Gallinek [13] to explain fear of ECT on the

basis of a temporary annihilation of the sense of familiarity with one's surroundings and involving a loss of personal orientation in space and time. Nowhere in the personal document presented, however, is there any discernible evidence which would tend to support such an "existentialistic" interpretation. This is not to deny the validity of such theorizing, but only to emphasize that—as with symptoms—fear reactions to ECT may be based on differing dynamic constellations, which may vary from patient to patient.

A study is currently underway to assess the hypothesized relationship between reaction to treatment and dynamics of illness. This study will analyze the four fears delineated previously in terms of, first, what is known of the patient's developmental history, and, second, what is known of his behavior in the interpersonal context of intensive psychotherapy. While it is not feasible at present to discuss the method and findings of this supplementary study, it is possible to indicate that the evidence to date strongly supports the contention that the emotional reactions to ECT of this particular patient are dynamically determined. Accordingly, it is suggested that reactions to ECT are not to be considered either as chance phenomena, and so subject to no interpretation, or as universal, and so subject to a monistic interpretation. Rather, it is proposed that particular emotional reactions to treatment have arisen because of their suitability to the individual patient's psychic economy and that their meaning lies within the unconscious realm of the patient's psyche. It is felt that only by an intensive study of individual cases can such emotional reactions to ECT be fully comprehended.

Summary

The diary of a patient undergoing electroconvulsive therapy (ECT) is presented and the fears of treatment expressed therein are delineated. Four fears are discussed: (1) fear of punishment; (2) fear of helplessness; (3) fear of humiliation, and (4) fear that the treatment might affect the patient's mind. The idiosyncratic, or unique, aspect of such fears is emphasized and the hypothesis advanced that the particular form and content of these fears were not the products of chance occurrence. It is suggested that the nature of such reactions to ECT is dynamically determined and that the meaning of these reactions can be comprehended best through an understanding of those mechanisms which lie within the unconscious realm of the patient's psyche.

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Comparative Lucid Intervals After Amobarbital, CO_2, and Arecoline in the Chronic Schizophrenic

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Introduction

It has been found by numerous investigators that reserpine inhibits the conditioned avoidance response in animals. When administered to man, reserpine produces symptoms of parasympathetic (muscarinic) stimulation. With these two facts in mind, Pfeiffer and Jenney[1] tested the effect of certain tertiary amine muscarinic stimulants on the conditioned avoidance responses of rats protected peripherally with atropine methylnitrate. The drugs arecoline, pilocarpine, and physostigmine were found to be effective inhibitors of the conditioned avoidance response. To test the correlation between the inhibition of the conditioned avoidance response in animals and the production of "lucid intervals"* in schizophrenic patients, arecoline was administered to schizophrenic patients. Two-thirds of the patients showed an apparent reversal of the schizophrenic symptoms for a period of 15 to 20 minutes.

Several of the arecoline-induced lucid intervals appeared as dramatic as those produced by the administration of amobarbital sodium (Amytal sodium) or by the inhalation of carbon dioxide. Both of these drugs have been known for some time to be effective in the production of temporary remission of schizophrenic symptoms. This report concerns more intensive investigations of the comparative effectiveness of arecoline, amobarbital, and carbon dioxide as adjuvants for psychiatric interviews of schizophrenic patients.

Methods

Twenty male and four female chronic schizophrenic patients, who had been hospitalized for 2 to 18 years, were chosen for these studies. Seven patients received the drugs in the order of arecoline, carbon dioxide, and amobarbital; seven others, in the order of carbon dioxide, amobarbital, and arecoline, and seven others, in the order of amobarbital, arecoline, and carbon dioxide. A two- to four-day interval was allowed between successive administrations of the three drugs in any one patient.

A. Dosages, Methods, and Rates of Administration of Drugs.—For the amobarbital interviews, from 150 to 500 mg. of 10% amobarbital sodium solution was administered intravenously at the rate of 5 to 10 mg. per minute. The injection of this solution was terminated when (1) the entire 500 mg. had been given or (2) the patient had become so narcotized that he was no longer accessible to interview.

For the carbon dioxide interviews a mixture of 30% carbon dioxide and 70% oxygen was administered by means of an open-inhalation apparatus. This was terminated when (1) a total of 75 breaths had been inhaled during a

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* The term "lucid interval" was first used by Bleckwenn in 1930 to describe the temporary antischizophrenic effect of amobarbital administered intravenously.[2] We continue to use this term, since it seems superior to the term "cerebral stimulation," "period of contact," "transient period of responsiveness," "stupor-free period," "mental response," "abreaction," "transitory accessibility," etc., all of which have been used by individual authors.[3-7] Undoubtedly, the best term would be "antischizophrenic effect," if we could be certain a "lucid interval" is a schizophrenia-diminished interval.

four- or five-minute period regardless of whether or not these had been inhaled consecutively, or (2) the patient became so resistive that the inhalation mask could no longer be maintained in firm contact with his face by moderate pressure.

For the arecoline interviews each patient was given a premixed subcutaneous injection of 15 mg. of arecoline and 3 mg. of atropine methylnitrate (AMN). The atropine methylnitrate was included to protect the patients from the peripheral effects of the parasympathetic stimulation by arecoline, such as excessive salivation, defecation, and pulmonary edema.

B. Interview Procedure.—Regardless of which drug was administered, the interview procedure was essentially the same.

Each of the patients was interviewed prior to the drugs, and an attempt was made to record his general appearance, facial expression, posture, degree of alertness and spontaneous movement, and speech content with regard to quality, quantity, and appropriateness. Then one of the three drugs was administered, and the patient's behavior, speech, and appearance in the postinjection period were recorded and compared with his behavior, speech, and appearance in the preinjection period and with his habitual mental status, which had been determined by a review of his hospital record and by the results of several interviews during the weeks prior to the tests.

C. Criteria for Evaluating the Quality of Lucid Intervals.—1. A patient's lucid interval was classified as "excellent" when the patient showed a marked degree of improvement in his willingness and/or ability to pursue conversational goals, to interpret simple proverbs correctly, to explain his course of action in various hypothetical situations, to discuss his activities, likes, dislikes, and plans for the future, to relate accurately the facts of his past history, and to view his present situation in terms of past events.

2. A patient's lucid interval was classified as "good" when he showed at least a moderate degree of improvement in those spheres listed under the criteria for the rating "excellent," except with regard to that portion of the interview dealing with his insight into his present situation, about which he could be totally ignorant or unwilling to talk and still have his lucid interval rated as "good." The rating "good" was also applied to those lucid intervals in which there was only a slight degree of improvement in the mental status of the patient with regard to the above spheres, provided at the same time he showed a marked degree of improvement in emotional outflow, as indicated by such behavior as laughing, crying, cursing, frequent sighing, facial and hand gestures, and other attempts at more forceful expression.

3. A patient's lucid interval was classified as "fair" when he showed only a slight or no perceptible change in those spheres of his mental status represented by the items listed under the criteria for the rating "excellent," provided there was at least a moderate degree of improvement in his emotional outflow and/or in his degree of alertness, as indicated by a newly acquired interest in exploring with hand and eye his own body and the objects surrounding him, or by a prompter responsiveness to questioning even if the content of his responses was essentially the same as that of the preinjection interview.

4. A patient's lucid interval was classified as "poor" when there was only a slight degree of improvement in his emotional outflow or in his degree of alertness.

5. The classification of no change is self-explanatory.

Results

A. Pharmacological Effects of Arecoline and AMN Mixture.—These effects included tachycardia, the rate in one patient being as high as 192 per minute, and a rise in both systolic and diastolic blood pressure of 15 to 40 mm. of mercury. One patient vomited 8 minutes after a dose of 15 mg. of arecoline and 3 mg. of AMN, and one patient vomited 20 minutes after a booster dose of 10 mg. of arecoline which had been given 15 minutes after the initial injection of arecoline and AMN. Two other patients complained of nausea but were not observed to vomit during two hours following a 25 mg. injection (initial dose and booster). As noted by Pfeiffer and Jenney,[1] "fine tremors, hyper-reflexia, yawning, sighing respiration, and exploratory movements of the hands about the face and head" and facial pallor (following an initial facial flush) were commonly observed. This last symptom, as well as the tachycardia observed, is attributed to the effects of the AMN. There was no occurrence of symptoms produced by the peripheral effects of muscarinic stimulation, i. e., sweating, salivation, or defecation.

B. Quality of Lucid Intervals.—On the basis of the criteria listed under "Methods and Materials," each of the 70 interviews of this study was evaluated according to the

Comparative Effect of Three Interview Drugs in the Same Patient Population

Lucid Intervals	Amobarbital		30% Carbon Dioxide		Arecoline and Atropine Methylnitrate	
	No. of Patients	Average Dose, Mg.	No. of Patients	Average Dose, No. of Breaths	No. of Patients	Average Dose, Mg. of Arecoline
Ratings						
"Excellent"	2 (9%)	315	1 (5%)	50	0 (0%)	
"Good"	6 (26%)	420	3 (13%)	50	3 (12%)	18
"Fair"	7 (30%)	443	9 (41%)	43	11 (44%)	22
"Poor"	6 (26%)	385	6 (27%)	47	7 (28%)	22
"No change"	2 (9%)	250	3 (14%)	44	4 (16%)	25
Totals	23*		22†		25‡	
Duration	20–80 min.		5–15 min.		5–30 min.	

* One patient did not receive amobarbital because obesity prevented venipuncture.
† Two patients steadfastly refused to breathe carbon dioxide.
‡ One patient was tested twice with the arecoline and atropine methylnitrate mixture.

quality of the resulting lucid interval. The results of this evaluation were summarized in the accompanying Table.

Comment

As shown in the Table, the precentage of patients who experienced useful lucid intervals was highest with amobarbital and lowest with arecoline and atropine methylnitrate injection. Thus, when the results are evaluated in the manner illustrated in the Table, it would appear that arecoline was the least effective of the three drugs for the production of lucid intervals in this particular group of schizophrenic patients; however, there were several persons in whom arecoline produced a lucid interval, rated as "fair" or better, which was better than that produced by one or both of the other two drugs. 1. Two patients experienced a better lucid interval with arecoline than with amobarbital. 2. Five other patients experienced a better lucid interval with arecoline than with carbon dioxide. 3. Three other patients experienced a better lucid interval with arecoline than with either amobarbital or carbon dioxide.

For the purpose of psychiatric interviews, a lucid interval of any degree less than "good," as defined above, is, it would seem, of little real value, and the only three arecoline-induced lucid intervals which received a rating as high as "good" were each matched by a better lucid interval occurring in the same patient when amobarbital was the test drug. Furthermore, 35% of the amobarbital-induced lucid intervals were rated as at least "good," as compared with only 12% of the arecoline-induced lucid intervals receiving this rating. Finally, it has already been noted that the amobarbital-induced lucid intervals were longer than the arecoline-induced intervals. Thus, according to the results of this particular study, amobarbital is definitely superior to arecoline as an interview drug.

Regarding the question of the superiority of carbon dioxide over arecoline, it is not possible to answer so definitely as it is in the case of amobarbital *vs.* arecoline. While the figures in the Table indicate that carbon dioxide is slightly more effective than arecoline in the production of lucid intervals, the difference between the percentages for the two drugs is not great. Also, the lucid intervals produced by carbon dioxide were of shorter duration than those produced by arecoline. Carbon dioxide had the further disadvantage of almost invariably causing the patient to become apprehensive and resistive to further testing regardless of whether a lucid interval was produced, whereas this apprehension and resistance to further treatment were never observed after an arecoline and AMN interview. For these reasons, therefore, it is felt that carbon dioxide and arecoline are probably about equally inferior to amobarbital as adjuvants

in psychiatric interviews of schizophrenic patients. Present trials of arecoline and AMN in normal human volunteers, undertaken to determine the effect on the EEG, have demonstrated that 3 mg. of AMN is an unnecessarily high dose. Arecoline 15 mg. may be given with 1 mg. of AMN, in which case the flushing, pallor, and tachycardia are greatly diminished. Arecoline compares poorly with amobarbital as an interview drug in both degree and duration of the lucid interval. However, arecoline is more convenient to administer, and either arecoline or amobarbital may be useful as a pretest to determine whether a lucid interval correlates in any way with the social rehabilitation produced by prolonged reserpine or chlorpromazine therapy.

Arecoline is still unique among drugs which produce a lucid interval in that its mode of pharmacological action is that of parasympathetic stimulation of the brain. Lucid intervals after amobarbital or carbon dioxide are accompanied by a complex depression of the brain, and their modes of action are therefore much more difficult to analyze. This clinical action of arecoline indicates the need for research studies on the naturally occurring metabolites which have a strong cerebral parasympathetic action and which may be more antischizophrenic than the presently available tranquillizing drugs.

Summary

A rigid experimental design was used to determine the relative effectiveness of amobarbital, carbon dioxide (30%), and arecoline as interview drugs in 24 chronic schizophrenics. Therapy was purposely staggered so that eight patients received one of the three agents as their first medication. The interviews were standardized, and definite criteria were established for rating the drug effects in five categories. The peripheral parasympathetic effects of arecoline were prevented by the simultaneous subcutaneous dose of 3 mg. of atropine methylnitrate. This dose is, however, unnecessarily large, and therefore 1 mg. is recommended. A "fair"-or-better lucid interval was obtained with amobarbital in 65% of the patients, with 30% carbon dioxide in 59% of the patients, and with arecoline plus atropine methylnitrate in 56% of the patients. The mixture last mentioned is of great interest because its action is that of parasympathetic stimulation of the brain, whereas both amobarbital and carbon dioxide are more complex in their pharmacological action. This comparative study indicates that more research effort should be expended on the naturally occurring metabolites which have cerebral parasympathetic stimulant action and which may be more antischizophrenic than the presently available tranquillizing drugs.

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Epinephrine and Arterenol (Norepinephrine) in Mental Disease

Plasma and Cerebrospinal Fluid Concentrations

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With improvements and advancements in methodology and precision instruments, the search for abnormal concentrations of various chemicals in patients with mental disorders has been intensified. A relationship of the sympatheticoadrenal system and endogenous epinephrine and arterenol (norepinephrine) to emotion and mental disease has been suggested by numerous investigators.[1-12]

Because of the repeated assertion that the reactivity of the sympatheticoadrenal system is altered in some mental disorders, quantitation of the plasma pressor amines seemed clearly indicated in certain psychiatric conditions. With the fluorometric method of Weil-Malherbe and Bone[13] and the modification devised in our laboratory,[14] it has been possible to quantitate epinephrine and arterenol in the plasma of normal subjects and psychiatric patients undergoing several forms of "stress" and treatment. In addition, the pressor amines in cerebrospinal fluid have been estimated in a variety of patients.

From the analysis of plasma extracts by the method of paper chromatography followed by elution and fluorometric quantitation, this fluorometric method appears to be rather specific. However, as we have stated previously,[15] it is probable that plasma contains substances other than epinephrine and arterenol which are extracted by the method of Weil-Malherbe and Bone and produce fluorescence that may cause a small error in the quantitation of these pressor amines.

In order to test the accuracy of the method, 16 recovery determinations were made in which known amounts of the substances to be assayed were added to plasma and then estimated as unknowns. For the assay of epinephrine, with a mean concentration of 10.0γ per liter, the standard deviation of the errors of determination was 1.4, or 14%, measured as a coefficient of variation. For arterenol, with a mean concentration of 18.1γ, the standard deviation of the errors was 4.0, corresponding to a coefficient of variation of 22%. For the assay of total epinephrine-like substance,* as was to be expected, since this

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Abridgment of portion of thesis submitted by Dr. Manger to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Medicine. A preliminary report of this investigation was presented at the XX International Physiological Congress, Brussels, Belgium, July 30 to Aug. 4, 1956.

* "Epinephrine-like substance" signifies the concentration equivalent to the fluorescence in the plasma if it were due entirely to epinephrine. Usually epinephrine and arterenol are present in plasma. Since we have found that the fluorescence of arterenol is only about one-third that of epinephrine, the epinephrine-like substance is less than the sum of the concentrations of epinephrine and arterenol when both are present.

analysis involves fewer technical manipulations, the error was smaller than that for either of the specific constituents; the mean concentration was 15.3γ and the standard deviation was 1.7, representing a relative error of 11%.

Effect of Mescaline and LSD-25

Historical Background.

In 1953 Liddell and Weil-Malherbe reported the effects of intravenous administration of methamphetamine hydrochloride (*d*-desoxyephedrine hydrochloride; Methedrine), 40 to 60 mg., and *d*-lysergic acid diethylamide (LSD-25), 40 to 60γ, on the mental processes and epinephrine-like substance in the blood of a group of patients with mental disorders.[16] After a brief initial period of relaxation, both drugs intensified the symptomatology and accentuated the clinical picture. In the doses used, methamphetamine seemed more effective in increasing tension and causing cataleptic phenomena and abreaction and in uncovering delusional material. Also, in schizophrenic patients methamphetamine induced hallucinations more readily than did LSD-25. Insomnia was frequent after use of methamphetamine, but rapid swings of mood with predominant euphoria were noted only after use of LSD-25. Similarities of changes in concentration of pressor amines were observed after administration of these drugs. For example, after administration of methamphetamine the concentration of epinephrine-like substance usually increased promptly and then decreased to less than the control value; later there was a slight secondary increase to more than the control value. Some of the patients given methamphetamine, however, experienced no initial increase in concentration of pressor amines but, rather, a decrease followed by an increase. Both these patterns of change in concentration were observed after intravenous administration of LSD-25, but the changes with this drug occurred more rapidly than with methamphetamine. When LSD-25 was administered orally to three patients, only the initial rise, followed by a fall and secondary rise in concentration of epinephrine-like substance, was observed. The rate of change in concentration was much more gradual after oral than after intravenous administration. Hyperglycemia was noted after the use of methamphetamine only if there was an initial increase of pressor amine, but no particularly significant rise in concentration of blood sugar was noted after use of LSD-25.

We were interested in comparing the changes in concentration of plasma pressor amines that follow the administration of mescaline and LSD-25 to normal subjects with corresponding changes in patients with mental disorders. A difference in the pattern of change between these two groups would demonstrate a derangement of physiochemical responsiveness in patients with certain mental disorders.

Procedure.

Samples of venous blood were obtained from fasting healthy male volunteers (all physicians) after an initial period of 20 to 30 minutes at rest. Immediately thereafter they were given either 400 mg. of mescaline or 50γ of LSD-25 orally.† Samples were again obtained from the antecubital vein approximately one-half, one, and two hours later. For greater accuracy, duplicate determinations of epinephrine-like substance were made on all samples except those drawn one hour after administration of the drugs. Both epinephrine and arterenol were quantitated in the samples obtained one hour after drug administration. The blood pressure and pulse rate were repeatedly determined. The subjects were required to remain seated during the period of observation, and psychologic, physiologic, and electroencephalographic changes were recorded. In addition, the reversibility of the induced psychoses by the administration of chlorpromazine was noted and has been reported on by Schwarz and associates.[17] ‡

† Neither mescaline nor LSD-25 caused any fluorescence when added in fairly large concentrations to samples of plasma, which were then quantitated in the usual way for epinephrine and arterenol.

‡ Key to correspondence of healthy volunteers receiving drug and represented in Tables 1 and 2 of this paper to those represented in Tables 1 and 2 of the paper by Schwarz and co-workers[17]:

TABLE 1.—*Plasma Pressor Amines, Blood Pressure (BP), and Pulse Rate (PR) Before and After Administration of Mescaline*

	Prominent Symptoms After Mescaline*	Control			After 400 Mg. of Mescaline Orally								
					½ Hour			1 Hour			2 Hours		
		ELS†	BP	PR	ELS†	BP	PR	ELS†	BP	PR	ELS†	BP	PR
	Healthy Volunteers Receiving Drug												
1	Expansiveness, floating sensations, very marked visual effects, nausea	2.7	128/82		4.0	110/80		3.7‡					
2	Expansiveness and feeling of well-being, marked disturbance in body image, synesthesias	1.1	110/78	78	2.2	118/88	53	1.2	112/76	52	1.8	106/72	53
3	Withdrawal, stupor-like, marked visual effects, synesthesias, vomited 25 min. after drug	1.2	120/88	78	1.8	128/92	80	1.4	122/80	80	1.0	118/88	80
4	State resembling agitated depression with multiple somatizations, nausea	1.5	156/108	80	1.0	168/98	76	1.0	152/108	76	1.6	141/98	78
5	Suspiciousness, auditory hallucinations, hyperacusis, synesthesias, nausea	0.8	116/78	68	1.1	122/88	68	0.8	120/89	70	1.2	146/118	64
6	State resembling agitated depression, many autonomic complaints, nausea	0.9	108/70	52	1.7	128/94	56	1.3	138/74	58	1.6	138/80	56
7	Withdrawal, blocking, neologisms, marked synesthesias, nausea	0.8	96/68	70	1.1	124/90	76	0.8	118/90	76	1.2	130/98	80
8	Suspiciousness, marked body-image disturbance, disfigured body complex, nausea	0.4	105/72	62	1.1	120/85	68	0.4	108/80	72	1.1	108/80	64
9	Simple withdrawal into contemplative-like state with visions, nausea	1.9	108/78	80	2.8	110/74	80	2.4	108/72	80	2.5	108/74	80
10	Some anxiety, moderate withdrawal, visions, somesthesias, nausea	0.8	118/80	52	1.5	116/86	52	1.0	118/80		0.8	118/83	64
	Mean	1.2	116/80	68.9	1.8	124/88	67.7	1.4	122/84	70.5	1.4	124/88	68.8
	Psychotic Patients Receiving Drug												
1	(Catatonic schizophrenia): mescaline facies, waxy flexibility increased	1.6	88/60	68	1.1	84/68	68	1.4	84/58	64	1.3	96/66	68
2	(Psychosis, grand mal epilepsy): mescaline facies, more talkative	2.1	104/72	80	1.9	106/58	84	2.1	104/68	76	1.9	102/60	86
3	(Paranoid schizophrenia): no change	1.7	118/78	76	1.8	124/76	68	2.0	116/80	80	1.7	120/80	84
4	(Simple schizophrenia): no change	2.3	120/52	96	2.1	108/54	88	1.3	122/58	86	1.6	126/54	84
	Mean	1.9	108/66	80.0	1.7	106/64	77.0	1.7	100/66	76.5	1.6	111/65	80.5
	Dog Receiving Drug												
1	Restless, struggling, barking, injected conjunctivas, slight ataxia	1.3			1.3			1.6			1.3		

		Healthy Volunteers Not Receiving Drug									
		1.6	108.72	1.6	108.76	1.4	118.84	1.6	114.84		
		1.0	108.70	1.4	102.68	1.3	104.68	1.2	98.64		
	Mean	1.3	108.71	1.5	105.71	1.4	111.76	1.4	106.74		

* Diagnosis prior to drug administration is given in parenthesis.
† E.L.S. epinephrine-like substance, micrograms per liter of plasma.
‡ Blood sample drawn one and one-half hours after mescaline was administered.

Table 1 (Mescaline)

No. of Subject	
Schwarz and Co-Workers	Manger and Co-Workers
2	1
4	2
1	3
3	4
5-10	5-10

Table 2 (LSD-25)

No. of Subject	
Schwarz and Co-Workers	Manger and Co-Workers
12	1
1	2
2	3
3	4
5-11	5-11

Under very similar conditions the effect of mescaline and, later, of LSD-25 was noted in four psychotic patients, who remained recumbent during the period of observation. The effect of these drugs on depth electrograms in two of these patients has been reported by Schwarz and associates.[19] § The effect of mescaline and LSD-25

Table 1 (Mescaline)

No. of Subject	
Schwarz and Co-Workers	Manger and Co-Workers
3	1
4	2

Table 2 (LSD-25)

No. of Subject	
Schwarz and Co-Workers	Manger and Co-Workers
3	1
4	2

on the concentration of plasma pressor amines in the dog was also noted.

Finally, blood samples from two healthy volunteers not receiving any medication were obtained at the same time intervals as those mentioned above and were analyzed for concentration of epinephrine-like substance.

The observations made are recorded in Tables 1 and 2.

Results.

The observations on concentration of pressor amines at various time intervals are graphically represented for mescaline and LSD-25 in Figures 1 and 2, respectively. There was no remarkable change in these concentrations in any of the groups

§ Key to correspondence of psychotic patients represented in Tables 1 and 2 of this paper to those represented in Tables 1 and 2 of the paper by Schwarz and co-workers[19]:

TABLE 2.—*Plasma Pressor Amines, Blood Pressure (BP), and Pulse Rate (PR) Before and After Administration of LSD-25*

	Prominent Symptoms After LSD-25*	Control			After 50 γ of LSD-25 Orally								
					½ Hour			1 Hour			2 Hours		
		ELS†	BP	PR	ELS†	BP	PR	ELS†	BP	PR	ELS†	BP	PR
		Healthy Volunteers Receiving Drug											
1	Detached, sense of timelessness	0.9	110/88	80	1.6	115/78		0.8	122/93		1.2	115/98	
2	Contemplative, daydreaming	1.6	106/78	72	0.9	112/72	64	1.5	104/74	64	1.1	108/70	60
3	Silly, facetious, expansive	2.8	104/78	68	2.7	96/64	70	2.2	102/70	76	2.5	106/70	68
4	Silly, inappropriate grinning	1.4	124/88	84	1.7	120/90	72	1.1	126/90	72	1.1	122/82	84
5	Megalomania, neologisms, synesthesias	2.9	112/74	70	2.1	118/70	62	1.0	124/76	66	0.7	120/70	72
6	Uncontrollable laughing, clang associations	2.1	108/72	68	2.3	96/70	64	1.7	104/70	64	2.3	104/70	78
7	Expansive, singing, joking, floating	1.0	112/82	64	0.9	102/78	68	0.5	100/76	80	0.5	110/80	80
8	Sense of unreality, grinning to self, pronounced visual effects	2.3	98/62	60	2.5	92/60	56	2.4	98/70	56	2.9	110/80	70
9	Ideas of reference, reminiscences, depersonalization	1.7	122/88	80	2.0	138/98	72	2.0	122/94	64	3.0	118/88	64
10	Preoccupied with somatic sensations, "out of contact and unreal"	1.5	104/84	64	1.6	96/66	64	1.5	102/82	60	2.5	108/84	64
11	Uncontrollable laughter, sense of incongruity, visual effects	2.0	118/78	80	1.7	118/80	84	1.2	110/74	72	1.8	118/80	76
	Mean	1.8	111/79	71.8	1.8	109/75	67.6	1.4	110/79	67.4	1.8	113/80	71.6
		Psychotic Patients Receiving Drug											
1	[Catatonic schizophrenia]: laughed, talked to self, brighter facies	1.6	100/70	62	1.7	100/70	64	2.4	102/68	64	2.0	108/72	74
2	[Psychosis, grand mal epilepsy]: little clinical effect	2.3	104/70	80	1.5	96/64	82	1.5	106/56	78	1.3	112/58	84
3	[Paranoid schizophrenia]: slight clinical effect	2.8	110/74	112	2.0	124/74	84	2.0	110/86	84	2.2	128/86	80
4	[Simple schizophrenia]: no change	2.6	128/78	100	2.1	126/74	80	1.6	110/70	72	1.7	122/68	72
	Mean	2.3	110/73	88.5	1.8	112/70	77.5	1.9	107/70	74.5	1.8	118/71	77.5
		Dog Receiving Drug											
1	Crying, barking, struggling, howling, chewing block of wood, restlessness	1.4			2.0			1.8			2.3		

* Diagnosis prior to drug administration is given in brackets.
† ELS, epinephrine-like substance, micrograms per liter of plasma.

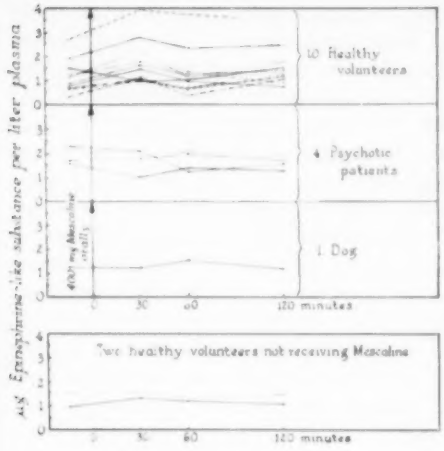

Fig. 1.—Effect of mescaline on plasma pressor amines.

studied except in the healthy volunteers one-half and two hours after receiving mescaline. At the one-half hour time interval the concentration of epinephrine-like substance in the plasma was greater than the control concentration in 9 of the 10 volunteers receiving mescaline. The elevation of the mean concentration of epinephrine-like substance one-half and two hours after administration of mescaline was found to be of definite statistical significance. However, because of the small series, this study should be extended to determine whether a clear-cut difference in this biochemical response to mescaline exists between normal and psychotic subjects.

In Table 3 are recorded the mean, the standard error of the mean, and the standard deviation for the concentration of epinephrine-like substance before (control value) and after administration of mescaline and LSD-25. Also recorded are similar determinations on the differences between the concentration of epinephrine-like substance one-half, one, and two hours after administration of mescaline and LSD-25 and the control concentration.

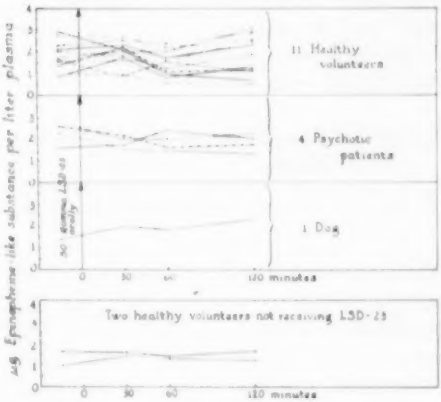

Fig. 2.—Effect of LSD-25 on plasma pressor amines.

TABLE 3.—*Statistical Data on Concentration, in Micrograms per Liter of Plasma, of Epinephrine-like Substance Before (Control Value) and After Administration of Mescaline and LSD-25*

			Hours After Drug Administered					
		Control	½	1	2	½	1	2
						Differences from Control		
				Mescaline				
10 volunteers	Mean	1.2	1.8	1.4	1.4‡	+0.62	+0.19	+0.38‡
	SEM*	0.21	0.30	0.30	0.17	0.16	0.12	0.11
	SD†	0.67	0.95	0.96	0.52	0.50	0.39	0.34
4 psychotics	Mean	1.9	1.7	1.7	1.6	−0.20	−0.22	−0.30
	SEM*	0.16	0.22	0.20	0.12	0.12	0.28	0.14
	SD†	0.33	0.44	0.41	0.25	0.24	0.56	0.29
				LSD-25				
11 volunteers	Mean	1.8	1.8	1.4	1.8	−0.018	−0.39	−0.05‡
	SEM*	0.20	0.17	0.18	0.27	0.14	0.18	0.28
	SD†	0.66	0.58	0.60	0.90	0.45	0.60	0.93
4 psychotics	Mean	2.3	1.8	1.9	1.8	−0.50	−0.45	−0.52
	SEM*	0.26	0.14	0.20	0.20	0.21	0.42	0.32
	SD†	0.53	0.28	0.41	0.39	0.42	0.84	0.64

* SEM, standard error of mean.
† SD, standard deviation.
‡ Calculations based on nine volunteers, with mean for control values of 1.0.

Inspection of Table 3 discloses that for the volunteers (normal subjects) treated with mescaline there is a rise in the concentration of epinephrine-like substance, whereas there is no rise, and in fact a decrease, in concentration in all other subjects given mescaline or lysergic acid. However, only the rise in plasma concentration of epinephrine-like substance in normal subjects one-half and two hours after administration of mescaline is statistically significant (the mean differences being 3.9 and 3.4 times their standard errors, corresponding to $P<0.001$).

Both epinephrine and arterenol were quantitated in the samples obtained one hour after the drugs had been given, and no deviation from the concentrations in normal subjects was noted.

Effect of Methacholine on Blood Pressure and Plasma Pressor Amines

Historical Background.

In 1948 Funkenstein and co-workers reported the various types of response of the systolic blood pressure that followed intravenous injection of epinephrine or intramuscular injection of methacholine (Mecholyl) in patients with mental disease and in normal subjects.[19] From their results they classified the responses into seven groups. They claimed that 80% of the normal subjects showed only a moderate or slight fall in systolic pressure with return to the preinjection level either promptly or within 25 minutes after intramuscular administration of 10 mg. of methacholine. However, only 20% of the mentally ill showed this type of response. They also stated that the response to electroshock therapy could be predicted more accurately from the response of the blood pressure to methacholine and epinephrine than from the psychiatric diagnosis. For example, the patients with mental disease who showed a marked fall in blood pressure and prolonged hypotension following the administration of methacholine—sometimes accompanied by a chill—appeared to respond most favorably to electroshock therapy. After such therapy the condition of 75% of the patients having a decreased reaction to methacholine and 90% of those having a decrease in basal blood pressure was improved. The following autonomic changes were frequently noted after electroshock therapy: (1) increased reaction to intravenous administration of epinephrine, (2) decreased response to methacholine, and (3) decreased basal blood pressure. Funkenstein and collaborators expressed the belief that the over-all effect of electroshock was to lower basal sympathetic tension and increase the reactivity of the sympathetic nervous system to stimulation. Decreased reactivity of the parasympathetic system was often a corollary.

In 1950 the same authors reported that changes noted in the response of their patients to epinephrine and methacholine were not specific but occurred with several types of therapy and spontaneous changes in the psychologic picture.[20] They further claimed that change in the psychologic condition of the patient seemed to accompany change in the physiologic response. Later, in 1951, they reported that the response of mental patients to electroshock therapy and insulin coma differed; they expressed the belief that testing psychiatric patients with epinephrine and methacholine could furnish information on which to base the choice of therapy.[21] In 1952 these authors reported that their psychiatric patients with elevation of blood pressure fell into two groups: (1) those in whom methacholine caused a marked fall in blood pressure that persisted through a 25-minute period and (2) those in whom methacholine caused only a slight fall in blood pressure, with return to the preinjection level within 25 minutes.[22] Their findings suggested that the marked and prolonged hypotensive response indicated the presence of an excess quantity of epinephrine in the blood. A slight fall with rapid restoration of homeostasis suggested

the presence of an excess quantity of arterenol.

Gellhorn studied the effects of methacholine in the cat and stated that the larger the dose the more prolonged the depressor action. He observed that the sympathetic response is evoked via the sinoaortic nerves [23] and occurs when the fall in blood pressure is considerable.[24] From additional studies he concluded that "the degree and particularly the duration of the hypotensive action of mecholyl and the reflexly induced discharges of the sympathetico-adrenal system depend on the hypothalamus." [25] He further stated [26]: "Apparently *conditions leading to increased sympathetic discharges of the hypothalamus as the result of electrical or chemical stimulation augment the responsiveness of the sympathetico-adrenal system to mecholyl and lead to a quicker return of the blood pressure and/or an overcompensatory hypertensive phase.*"

Procedure.

In view of the findings and hypotheses of the above investigators, we decided to study the effect of the intramuscular administration of 10 mg. of methacholine on the concentration of plasma pressor amines in patients with various psychiatric conditions. Twenty-one subjects (all fasting) were studied, and the observations made are presented in Table 4. In most of these patients, an indwelling needle equipped with a stylet was used so that blood samples could be obtained at any desired time without repeated venous punctures. Only two of these subjects (17 and 20) had hypertensive basal blood pressures.

Results.

The three characteristic types of blood pressure response to the administration of methacholine are shown in Figure 3; the records are from three different subjects. The response of the normoreactor, following intramuscular administration of 10 mg. of methacholine, consists of a drop of the systolic blood pressure with restoration to basal level within 10 minutes. The response of the hyporeactor induced by methacholine consists of a drop in systolic blood pressure without restoration to basal level within 10 minutes. The response of the hyperreactor

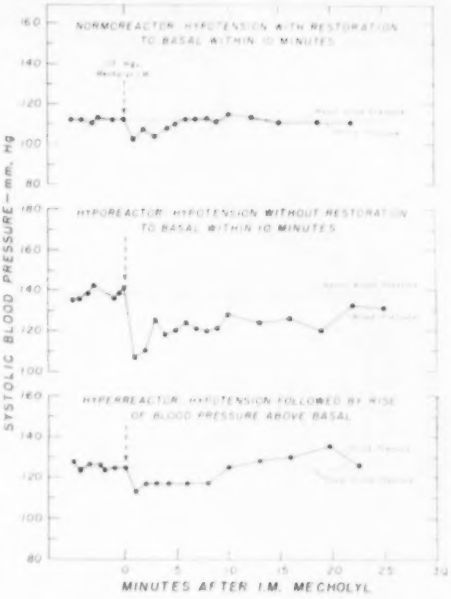

Fig. 3.—Types of blood pressure response to administration of methacholine.

is characterized by a drop in blood pressure followed by a rise above basal level.

These are empirical classifications which represented the blood pressure responses of nearly all the subjects tested. One subject, after injection of methacholine, exhibited a slight initial rise in blood pressure followed within one to two minutes by a fall in pressure below and subsequent recovery to the basal level. This type of blood pressure response was not mentioned by Funkenstein and co-workers [19,22] and is not represented by any of our three classifications. Only Subject 1 (Table 4) (normal man, age 34) reacted in this manner, and, since the subsequent pattern of blood pressure response was of the hyporeactor type, he was classified in the hyporeactor group. Another man (Subject 3), age 37, had an immediate and persistent rise in blood pressure following injection of methacholine, and only gradually (after seven minutes) did the pressure return to the basal level. This latter response was considered hyper-

TABLE 4.—*Plasma Pressor Amines and Blood Pressure Response After Administration of 10 Mg. of Methacholine*

Subject *	Age, Sex	Diagnosis † and Prominent Symptoms	Reaction ‡	Pressor Amines, Micrograms per Liter of Plasma §					Six-Month Follow-Up ¶
				Before Methacholine		After Methacholine, Min. ‖			
						1-3	3-5	5-10	
1	34 M	[Normal]: none	HO	ELS E A	1.3 0.1 4.5	1.9 0.0 7.0	1.9 0.5 5.2		Normal
2	32 M	[Normal]: none	N	ELS E A	2.4 0.0 8.8	1.7 0.3 5.1	1.9 0.0 7.0		Normal
3	37 M	[Normal? thyrotoxicosis?]: mild heat intolerance	HR	ELS E A	3.0 1.3 6.2	2.3 1.1 4.3	1.9 1.3 2.3		Found to be hyperthyroid
4	38 M	[Personality disorder]: sexual deviation	N	ELS E A	0.8 0.0 2.9	0.9 0.1 2.8			Tuberculosis suspect
5	20 M	[Personality disorder]: none	HR	ELS E A	1.1 1.0 0.4	1.8 1.4 1.5	1.8 1.8 0.0		Condition unchanged
6	35 M	[Reactive depression]: tense, insecure, deep fear and guilt, takes recourse in alcohol	HO	ELS	1.4	1.8	1.0	1.7	No response to therapy: CO_2, chlorpromazine, reserpine, or EST
7	52 M	[Obsessive-compulsive]: anxious, depressed, suicidal, groaning	HO (N)	ELS	2.0	1.8	2.6	1.6	Greatly improved by 31 ESTs, and chlorpromazine
8	47 F	[Reactive depression]: anorexia, fearful, insomnia, panics, depressed, choking, somatic complaints	HO	ELS E A	1.0 0.0 3.7	1.1 0.2 3.2	1.2 0.3 3.5		Slight improvement with 14 ESTs; signed out against advice; fearful of treatment
9	59 M	[Psychophysiologic gastrointestinal reaction]: nervous, upset, worried, somatic complaints	HR	ELS E A	2.0 0.0 7.3	1.5 0.7 2.9	1.5 0.1 5.1		Mild improvement after 14 ESTs
10	48 M	[Reactive depression]: anorexia, suicidal ideas	HR	ELS	1.3	0.8			Complete recovery after 11 ESTs
11	19 M	[Schizophrenia, chronic undiff. type]: withdrawn, hypoactive, depressed	HO	ELS	1.7	1.8	1.5	1.3	Moderate improvement after 12 ESTs
12	40 M	[Schizophrenia, paranoid]: bizarre behavior, auditory hallucinations, neglects self, suicidal	HO	ELS E A	1.8 0.0 6.6	1.4 0.2 4.3			Moderate improvement on ESTs
13	61 M	[Reactive depression]: agitated, worried, guilt feelings	HO	ELS E A	1.0 0.0 3.7	1.2 0.0 4.4	1.5 0.1 5.2		Improved on EST

14	45 F	[Manic-depressive]: self-accusatory, depressed almost mute, agitated	HO	ELS	0.7		1.4		Greatly improved on chlorpromazine
				E	0.4		0.1		
				A	1.1		4.9		
		(better than ever before)	(N)	ELS	(2.6)	(2.8)	(2.8)		
				E	(0.0)	(1.5)	(1.2)		
				A	(9.5)	(4.8)	(5.9)		
15	40 F	[Manic-depressive]: depressed, mute, somewhat fearful	HO	ELS	1.3	2.0	1.6		Moderate improvement on chlorpromazine, and later rapid improvement on EST
				E	0.9	1.9	0.9		
				A	1.3	0.5	2.6		
			(N)	ELS	(2.1)	(2.1)	(2.7)		
				E	(0.7)	(0.2)	(0.5)		
				A	(5.1)	(7.0)	(8.0)		
16	29 F	[Schizophrenia, chronic undiff. type]: depressed, worried, restless, withdrawn, neglects self	N (HR)	ELS	1.0	1.2			No change after 5 EST; later clinical improvement after 21 more ESTs
17	33 M	[Schizophrenia, paranoid]: delusional, restless, combative when provoked	HR (HO)	ELS	1.3	1.2	1.4	1.6	Much improvement but not complete recovery after 13 ESTs
18	36 M	[Schizophrenia, schizoaffective]: suicidal, withdrawn, delusions of reference	HR	ELS	1.8	1.7	1.4		Improving on EST
				E	0.0	0.4	0.0		
				A	6.6	4.8	5.1		
19	22 F	[Schizophrenia, acute undiff.]: paranoid delusions, auditory hallucinations, ideas of reference	HR (HR, almost N)	ELS	1.5	1.5	1.2	1.4	Very much improved by psychotherapy
20	32 M	[Manic-depressive]: overactive, restless, silly, talkative	HR	ELS	1.9	1.9		2.2	Improved after chlorpromazine and EST
			(HR, then N)	ELS	(1.1)				
				E	(0.0)				
				A	(4.0)				
21	33 M	[Schizophrenia, paranoid]: delusions of persecution	HR	ELS	2.8	2.4	2.5		Only slight improvement on EST
				E	0.5	0.0	0.0		
				A	8.5	8.8	9.2		

* Subjects 1 and 2, normal persons; Subject 3, normal person or one with possible thyrotoxicosis; Subjects 4 and 5, patients with personality disorders; Subjects 6 through 10, patients with psychoneurosis; Subjects 11 through 21, patients with psychosis.

† Diagnosis prior to drug administration is given in brackets.

‡ HO, hyporeactor; N, normoreactor; HR, hyperreactor; ( ), after treatment.

§ ELS, epinephrine-like substance; E, epinephrine; A, arterenol.

‖ EST, electroshock therapy.

1 to 3 = from start of 2d minute to end of 3d; 3 to 5 = from start of 4th minute to end of 5th; 5 to 10 = from start of 6th minute to end of 10th.

TABLE 5.—*Blood Pressure Reaction and Per Cent Change* in Epinephrine-like Substance in Plasma Following Intramuscular Administration of 10 Mg. of Methacholine*

Type and Condition of Reactor	Subjects	Epinephrine-like Substance	
		After 1-3 Min.	After 3-5 Min.
Hyporeactor			
Normal	1	46.2	46.2
Psychoneurosis	3	6.8	9.1
Psychosis	5	10.3†	27.6†
Normoreactor			
Normal	1	—29.2	—20.8
Personality disorder	1	12.5	—
Psychosis	1	20.0	—
Hyperreactor			
Normal? [thyrotoxicosis?]	1	—23.3	—36.7
Personality disorder	1	63.6	63.6
Psychoneurosis	2	—30.3	—25.0
Psychosis	5	— 6.5†	—12.2†

* The mean change from the corresponding control values expressed as per cent of control mean. Only values followed by a dagger (†) are statistically significant, since all other values are based on only three or less determinations. 1-3 = from start of 2d minute to end of 3d; 3-5 = from start of 4th minute to end of 5th.

reactor in type, though atypical.‖ All the subjects had excess salivation and experienced profuse sweating within one minute after methacholine was administered intramuscularly.

Table 5 reveals the blood pressure reaction and per cent change in epinephrine-like substance in blood samples secured one to three and three to five minutes after methacholine had been given intramuscularly. Only 1 of the 11 psychotic patients and none of the 5 psychoneurotic patients showed the blood pressure response of a normoreactor. Analysis of the results revealed no apparent change in concentration of plasma pressor amines that was consistent with any special pattern. There was no apparent correlation of the subjects' diagnosis with the type of blood pressure reaction to methacholine, and there was no indication that the type of blood pressure response was related to the concentrations of epinephrine and arterenol in the plasma.

Effect of Electroshock Therapy on Blood Pressure and Plasma Pressor Amines

Historical Background.

The effect of electroshock therapy on the concentrations of plasma epinephrine and arterenol in man was reported in 1955 by Weil-Malherbe.[27] He also cited observations by others that in various animals electroshock was followed by a rise in blood pressure, hyperglycemia, lymphopenia, eosinopenia (in psychotics and psychoneurotic patients), pupillary dilation, contraction of the nictitating membrane, and depletion of pressor amines in the adrenal medulla. Weil-Malherbe found that without previous medication the application of 90 to 120 volts for 0.4 to 0.5 second caused an increase in both epinephrine and arterenol in patients. After premedication with hexobarbital sodium soluble (Hexobarbitone), the concentration of both substances

‖ In a series of 100 tests with methacholine, one of us (C. W. B.) encountered this type of immediate paradoxical rise of blood pressure four times in four different patients. All four showed marked anxiety either as the main symptom of their illness or because it had been precipitated by electroshock or carbon dioxide inhalation therapy. After the anxiety had diminished or disappeared as a result of therapy, the paradoxical rise did not again manifest itself. A further possible explanation of this atypical reaction suggested itself five months after it had been observed in Subject 3 (Table 4), when his already existing symptoms of heat intolerance and fatigue became more marked, persistent tachycardia developed, and a diagnosis of toxic goiter was made. There was no anxiety at the time of this methacholine test. A repeat test, however, four months after treatment with radioactive iodine, which resulted in marked clinical improvement and considerable drop in the basal metabolic rate, showed a response typical of the group with normal reactivity to methacholine.

TABLE 6.—*Effect of Electroshock on Blood Pressure and Plasma Pressor Amines in Twelve Psychotic Patients* *

Patient	Age, Sex	Diagnosis and Prominent Symptoms †	Physical Examination ‡	Electroshock Therapy §
1	38 F	[Schizophrenia, paranoid]: extremely agitated	Normal (100/60; 70)	8th EST, 500 ma., 0.5 sec.; no twitchings
2	34 F	[Schizophrenia, catatonic]: very withdrawn and negativistic	Normal (110/60; 72)	21st EST, 450 ma., 0.5 sec.; Grade 3 reaction
3	40 M	[Schizophrenia, paranoid]: somatic delusions, moderate depression	Normal (120/80; 72)	2nd EST, 500 ma., 0.5 sec.; Grade 2 reaction
4	55 M	[Psychotic depressive reaction]: paces floor, insomnia, weight loss	Normal (160/80; 72)	4th EST, 450 ma., 0.5 sec.; Grade 2 reaction
5	45 F	[Schizophrenia, paranoid]: ideas of persecution, flat affect	Normal (122/82; 88)	7th EST, 500 ma., 0.5 sec.; Grade 2 reaction
6	50 M	[Schizophrenia, chronic undiff.]: mute, silly grin; masturbates	Thrombophlebitis, left leg (142/84; 92)	9th EST, 575 ma., 0.7 sec.; Grade 4 reaction
7	73 M	[Psychotic depressive reaction]	Normal (134/78; 82)	12th EST, 550 ma., 0.7 sec.; Grade 1 reaction
8	32 M	[Schizophrenia, chronic undiff.]: halting, illogical speech; flat affect; many mannerisms	Thoracic kyphoscoliosis (100/70; 72)	7th EST, 450 ma., 0.5 sec.; Grade 1 reaction
9	36 M	[Schizophrenia, paranoid]: delusions of persecution, had threatened to kill mother	Normal (120/90; 76)	30th EST, 550 ma., 0.5 sec.; Grade 2 reaction
10	36 M	[Schizophrenia, schizoaffective]: attempted suicide by sticking forks in head	Dermatographia (110/70; 80)	1st EST, 500 ma., 0.5 sec.; Grade 3 reaction
11	25 M	[Schizophrenia, paranoid]: hears gypsies talking to him	Marked scoliosis (105/75; 76)	10th EST, 500 ma., 0.5 sec.; no twitchings
12	31 F	[Mild mental deficiency, idiopathic, with psychotic reaction; I.Q. 76]: Believes people trying to kill her, is homicidal—bilateral prefrontal lobotomy 8 yr. ago, without improvement	Prefrontal lobotomy scar (132/85; 78)	7th EST, 500 ma., 0.5 sec.; Grade 2 reaction
		Mean of total and standard error of mean		

* Abbreviations: BP, blood pressure; EST, electroshock therapy; ELS, epinephrine-like substance; Epi., epinephrine; Art., arterenol; Ma., milliamperes.
† Diagnosis prior to electroshock treatment given in brackets.
‡ Blood pressure and pulse rate in parentheses.
§ Grade 1, slight twitching; Grade 2, moderate muscular activity; Grade 3, marked muscular activity; Grade 4, generalized convulsive seizure.
# Concentrations prior to administration of premedication—all other quantitations were made after 4 ml. of a 2.5 % solution o thiopental sodium and 20 mg. of succinylcholine chloride were administered intravenously.

became elevated subsequent to the application of electroshock therapy, but to a less degree than without premedication. The addition of a muscle paralyzant to this preliminary medication did not alter the liberation of pressor amines.

Procedure.

We have quantitated the concentration of epinephrine and arterenol in samples of blood obtained immediately before and as soon after electroshock (within one to two minutes) as practicable in 12 psychotic patients (Table 6). All of these patients were given 4 ml. of a 2.5% solution of thiopental sodium and 20 mg. of succinylcholine chloride just prior to electroshock to minimize the muscular contractions.

Results.

The effect of electroshock on plasma pressor amines and blood pressure is graphically represented in Figure 4, where the results appear in the same order as in Table 6. It is apparent that electroshock invariably causes an elevation in the concentration of epinephrine, whereas the arterenol increased in seven and decreased in five patients. The epinephrine-like substance increased in all patients except in Patient 4, who had a slight decrease owing to the diminution of arterenol. In Patients 1 and 2 the concentration of epinephrine decreased and the concentration of arterenol increased follow-

Response to EST at Present	Before EST				After EST			
	BP	ELS	Epi.	Art.	ELS	Epi.	Art.	BP
Remission	100/72	2.0 / 1.7	1.0 / 0.0	3.7 / 6.2	3.2	1.4	6.6	120/80
Poor; still withdrawn and apprehensive	120/80	1.0 / 1.2	0.5 / 0.2	1.7 / 3.8	2.8	1.3	5.5	138/80
Fair; fewer somatic delusions	150/75	1.1	0.2	3.3	1.6	0.7	3.2	180/70
Remission	130/90	3.0	0.1	10.6	2.5	1.0	5.6	140/90
Fair; less anxiety but still quite paranoid	100/85	1.3	0.4	3.3	2.6	0.7	7.0	175/90
Fair to good; not as retarded and repressed, eating and gaining weight	130/75	2.2	0.7	5.4	4.2	1.3	10.6	170/95
Good; less retarded and depressed, no longer stuporous and incontinent of urine	108/58	1.6	0.0	5.9	2.4	1.1	4.7	180/95
Poor; no change, same after 18th EST	115/75	1.0	0.0	3.7	2.0	0.9	4.0	118/75
Poor; no change		1.3	0.1	4.3	2.2	1.4	2.8	
Fair; less depression	145/80	1.9	0.0	7.0	3.4	2.5	3.3	170/10
Remission; rapid response to EST	125/75	1.5	0.3	4.4	4.6	2.5	7.7	140/70
No improvement	135/70	3.3	1.3	7.3	5.8	3.1	9.9	148/69
	124/76	1.8±0.21	0.28±0.11	5.4±0.62	3.1±0.35	1.5±0.23	5.9±0.74	153/83

ing premedication with thiopental (Pentothal) sodium and succinylcholine (Anectine) chloride, a muscle relaxant. Samples prior to premedication were not obtained in the remaining patients, and therefore the significance of the alterations of concentration of epinephrine and arterenol in Patients 1 and 2 following administration of thiopental and succinylcholine is uncertain. Patient 2 was acutely disturbed when the blood sample was obtained, just before premedication. In all patients the systolic blood pressure was immediately increased by electroshock, whereas the diastolic response was variable. It is noteworthy that the patients showing no clinical improvement invariably had only very slight changes in blood pressure.

Pressor Amines in Cerebrospinal Fluid

Historical Background.

In 1954 Weil-Malherbe and Liddell first quantitated epinephrine and arterenol in

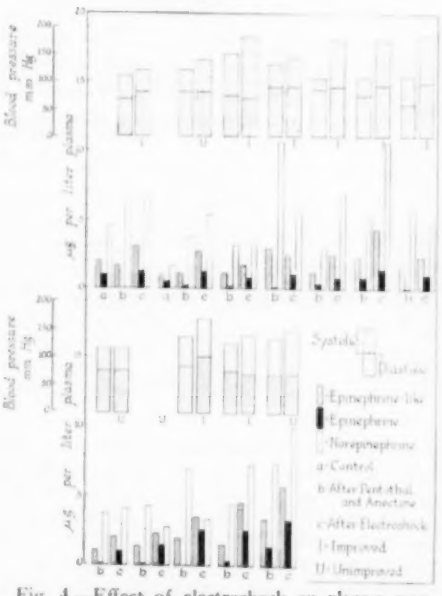

Fig. 4.—Effect of electroshock on plasma pressor amines and blood pressure in 12 psychotic patients.

cerebrospinal fluid.[28] The concentration of pressor amines in fluid removed at encephalography was determined in nine patients with suspected organic lesions of the brain and in nine male schizophrenic patients, three of whom had undergone leukotomy. They found that the concentration of epinephrine and of arterenol in cerebrospinal fluid was the same in the two groups, but lower than in venous plasma.

The ratio of epinephrine to arterenol in the cerebrospinal fluid and plasma was the same in the two groups, epinephrine representing 25% of the sum of these pressor amines. However, the plasma concentration of pressor amines was lower in schizophrenic patients than in those without schizophrenia. It was concluded that cerebrospinal fluid is not merely an ultrafiltrate of plasma but, rather, is a product of epithelium with specific secretory functions. They also cited the work of Walter, in 1929, which indicated a decrease in permeability of the blood-brain barrier, as measured by the bromide test, in schizophrenia. Accordingly, they would have expected a decrease in the concentration of pressor amines in the cerebrospinal fluid of the schizophrenic patients (if the level of these amines depended on the same mechanism as that measured by the bromide test), especially since the plasma concentrations were lower in the schizophrenic patients than in other subjects.

Procedure.

We quantitated the epinephrine-like substance in the cerebrospinal fluid, obtained by introducing a needle into the cisterna magna, of 22 patients (Table 7).¶ In all of these patients except one, with a chronic brain syndrome, the results of routine examination of the cerebrospinal fluid, including cell count, determination of total protein, and Wassermann test, were normal. The mean and standard deviation of the mean were determined for each group.

Results.

The findings indicate that the patients with mental deficiency have a lower mean concentration than the other groups, for instance, 0.8γ per liter for mental deficiency as contrasted with 1.2γ for personality disorder. However, analysis of our results shows that the differences in concentration of epinephrine-like substance in the cerebrospinal fluid of the five groups studied are not statistically significant in light of the considerable variability of the values and the small number of patients included.

¶ With the method of Weil-Malherbe and Bone, the recovery of epinephrine and arterenol from cerebrospinal fluid was found to be about 10% less than that from plasma. A correction for this recovery deficit was made when the concentrations in the cerebrospinal fluid were calculated.

TABLE 7.—*Epinephrine-like Substance in Cerebrospinal Fluid, Micrograms per Liter*

Personality Disorder (3 Patients)	Psychoneurosis (3 Patients)	Psychosis (9 Patients)	Chronic Brain Syndrome * (5 Patients)	Mental Deficiency (2 Patients)
0.6	0.8	0.7	0.4	0.8 †
1.6	1.1	0.9	0.8 ‡	0.9
1.6	1.8	0.9	0.9	
		0.9	1.2	
		0.9	1.8	
		1.0		
		1.2		
		1.3		
		1.7		
Mean § 1.2±0.3	1.2±0.3	1.1±0.1	1.0±0.2	0.8±0.1

* Chronic brain syndrome=organic disease of the brain.
† Cause of mental deficiency unknown.
‡ Cerebrospinal fluid: 120 mg. of protein per 100 cc. and colloidal gold reaction positive; normal in all other patients.
§ Number after ± is standard error of mean.

Comment

Effect of Mescaline and LSD-25.—The significance of the increase in the mean concentration of epinephrine-like substance in the plasma of normal subjects one-half and two hours after the oral administration of mescaline is uncertain. It is attractive to wonder whether some of the symptomatology which the drug produced in these subjects could have been related to an aberration of pressor amine metabolism. The fact that no increase in the mean concentration of epinephrine-like substance occurred in four patients with mental disease after administration of mescaline suggests that a difference may exist between physiochemical responsiveness of some psychiatric patients and of normal subjects.

Effect of Methacholine on Blood Pressure and Plasma Pressor Amines.—It is apparent that 10 mg. of methacholine given intramuscularly did not significantly alter the concentration of epinephrine-like substance. This was not surprising, since the hypotension following administration of this drug is usually slight and apparently not adequate to initiate a strong sympathetico-adrenal discharge in order to establish homeostasis. It will be recalled that Gellhorn's observations on the release of pressor substance after administration of methacholine were made in the cat, and he indicated that pressor substance was liberated after a "considerable" drop in blood pressure.[24] In the presence of marked hypotension it has been found by chemical quantitation that there may be considerable liberation of pressor amines.[29] It is also known that acetylcholine and some related substances can cause liberation of these amines.[30,31] The dose of methacholine given to our subjects may have been too small to cause significant secretion of pressor amines by the sympatheticoadrenal system. Also it is possible that liberation of a small amount of pressor substance from sympathetic nerve terminals may have occurred within the tissues where it was almost entirely destroyed, with little or none reaching the blood.

We have not found any evidence to support the concepts expressed by Funkenstein and co-workers or Gellhorn that the methacholine test is a measure of sympatheticoadrenal activity. At least the results of this test as described for man did not appear correlated with the concentration of plasma pressor amines in this small series.

Effect of Electroshock on Blood Pressure and Plasma Pressor Amines.—It had been hoped that the responsiveness of the sympatheticoadrenal system to electroshock (as reflected by the increase in plasma pressor amines) might be used as a prognostic guide. It is evident that the amount of pressor amines liberated or the blood pressure response following electroshock could not be correlated with the clinical state of the patient or the severity of muscular contractions at the time of therapy. However, whether any prognostic information can be gained from quantitating plasma pressor amines in psychotic patients undergoing electroshock therapy cannot be conclusively settled without repeated observations in a much larger series of patients.

Pressor Amines in Cerebrospinal Fluid.—All the mean concentrations of epinephrine-like substance in cerebrospinal fluid were lower than the mean plasma concentrations in both normal and psychotic subjects. The finding that the patients with mental deficiency have a lower mean concentration of epinephrine-like substance than the other groups studied is interesting in view of the report by Weil-Malherbe[32] that the mean concentration of plasma epinephrine is lower in patients with mental deficiency than in those with other conditions studied. However, quantitation of pressor amines in the cerebrospinal fluid of a larger number of subjects is indicated before any conclusions can be drawn.

Summary

A modification of the fluorometric method of Weil-Malherbe and Bone was used to

quantitate pressor amines in venous plasma of healthy volunteers and patients with mental disease, and in cerebrospinal fluid of subjects with various psychiatric conditions. After control samples of blood were obtained, 10 healthy volunteers and 4 psychotic patients in basal state were given 400 mg. of mescaline orally and blood samples drawn one-half, one, and two hours thereafter. An identical study was made on 11 healthy volunteers and 4 psychotic patients after oral administration of 50γ of lysergic acid diethylamide (LSD-25). Personality disturbances occurred in all volunteers; yet little change was observed in psychotic patients. No remarkable change in blood pressure or pulse occurred. The mean concentration of epinephrine-like substance in the plasma in the healthy volunteers was significantly increased one-half and two hours after administration of mescaline. There was no rise in mean concentration of epinephrine-like substance in any other subjects given mescaline or lysergic acid.

Intramuscular administration of methacholine (10 mg.) in 18 psychiatric patients and 3 healthy volunteers caused no significant change, from control values, in concentration of epinephrine-like substance in samples obtained at intervals ranging from one to five minutes after the drug had been administered and after the blood pressure changes and other effects of methacholine were evident.

All 12 patients given electroshock therapy had a significant transient increase of plasma epinephrine, whereas arterenol increased significantly in only 5. After electroshock, the plasma pressor amines frequently reached the concentrations that were obtained in some patients with pheochromocytoma, renal insufficiency,[15] increased intracranial pressure, and lymphoma.[33]

In 22 patients with psychoses, psychoneuroses, and personality disorders the concentrations of epinephrine-like substance in cerebrospinal fluid were similar; however, the mean concentrations in the cerebrospinal fluid were slightly lower than the mean concentrations in plasma.

Concentrations of plasma pressor amines in patients with mental disease were similar to those in normal subjects.

Dr. H. P. Rome and Dr. C. W. Moffett gave advice in this study.

Section of Publications, Mayo Clinic.

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Psychoanalytic Theories of Activity-Passivity Conflicts and of the Continuum of Ego Defenses

Experimental Verification, Using Reserpine and Chlorpromazine

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Psychoanalytic research has usually been conducted through the analysis of individual cases. This has yielded gratifying results. It is rare to find experiments using the scientific technique of the inductive experiment which directly apply to the data obtained by psychoanalysis. This is not surprising, since a psychological technique is needed to obtain psychological data. The older and more conventional branches of experimental science have, as a result, not always looked with favor or acceptance on the findings of psychoanalysis.

Projects and Their Aims

In investigating the effects on affect of reserpine and chlorpromazine in the wards of the psychoanalytically oriented psychiatric unit of a general hospital (Queen Mary Veterans' Hospital), experimental evidence was accidentally obtained which verified psychoanalytic concepts of activity-passivity conflicts[2,4,8] and of the continuum of ego defenses.[1,3,7,13]

Fifty-five specially selected patients with marked disorders of affect were studied with reserpine for a year. Concomitantly, 35 patients received chlorpromazine because of various therapeutic indications, on a nonresearch basis. The research design,[9,10] results, and conclusions of this work have been reported in detail elsewhere.[9-12] Only the points relevant to this paper will be mentioned here. The project was designed to find what the physiological and pharmacological effects of these drugs were in the human, and to see what these effects then did to the emotion displayed by the patient and/or the physiological concomitants of emotion. Psychoanalytic knowledge was used to evaluate, control, and interpret the interpersonal, social, and psychological factors involved.

Findings—Fourteen patients in the above-mentioned groups developed psychosis, or further psychotic deterioration, or enhanced anxiety. By way of contrast, two of the many patients who did well with essentially the same physiological effects and psychodynamic constellations were reported. The detailed report on these patients has been published elsewhere,[12] and the present paper is concerned only with those aspects of ego psychology and of activity-passivity conflicts shown by this study.

The physiological effects of the drugs were present in both those who did well and those who were made worse (i.e., in all 90 patients). A standard physiological action of the drugs, in the doses used, was to make the patient feel weak, tired, sometimes dizzy, and incapable of mobilizing formerly available energy into physical and muscular activity. The patient felt "slowed down" or "chemically held down."

These drugs effect large areas of human activity linked with the expression of affect, and of libidinal and aggressive energy, that is to say, the areas of being able to relate to oneself, or to others, through the ability to control and use one's own body, or through muscular activity; or to be extroverted. In varying degrees these drugs removed access to one or all of the above-

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mentioned means of sublimation or displacement.

When a patient was not psychologically threatened by these effects—good and well. Patients became clinically worse when, through limiting of the above outlets, important defenses, necessary for that patient's self-esteem and reassurance, or for his confidence in the integrity of his own body (i. e., body image) were removed (for details, see Sarver-Foner and Ogle [12]).

Another important consideration was the regular production by these drugs of various side-effects and toxicity. They tended to hit at organ systems, such as the gastrointestinal tract (nausea and vomiting, nausea, and diarrhea); the upper respiratory tract (nasal stuffiness), and the skin (erythema and flushing), as well as to produce dryness of the mouth, occasional dizziness, etc. Here, again, this effect was psychologically threatening and produced a rupture of the ego and further regression of these defenses in certain patients.

Report of a Case

An abbreviated case history of one such patient is given.

Situation on Admission.—A 25-year-old, white, Roman Catholic, single army officer was admitted to Queen Mary Veterans' Hospital with the following history.

He had been A. W. L. from his unit, a newly forming one, and had run up enormous debts without making any attempt to settle them. He had cashed bad checks and had drunk to excess on many occasions. His superiors had advised him to settle his debts or face disciplinary action and dismissal.

He was moderately depressed and displayed perplexity, ambivalence, and indecision as to what he should do about his situation. When his indecision had become marked, he went A. W. L. "to think things over." He was a tall, extremely well-built, good-looking man, who looked his stated age and who took pride in keeping himself in the peak of physical condition.

Onset of Illness.—Commissioned a little more than a year prior to admission, he had been happy as a private and junior N. C. O., but unhappy as an officer. Formerly, he had idealized officers. He had visualized them as strong men and leaders, who were moral, cleancut, good, self-sacrificing, idealistic, and dedicated men. He looked forward to joining this company. He became disillusioned when he saw some of his fellow officers as they really were—human beings with human needs. He had no real friends among them, since he was ill at ease in their presence. Nor did he have much work to occupy him, since in a forming regiment the drill and training instructors were doing most of it. In contrast to this, his N. C. O.'s career had been a very active one. He had been a paratrooper instructor who was always kept busy. He said that his evenings were spent "polishing boots with my buddies while we drank cokes, smoked, and talked." His uniform had "always been pressed and [his] boots shined." He took pride in his appearance, worked very hard, and was contented when others made decisions for him. "I was a good soldier and proud of myself." He had many occasional girl friends but was never really serious with any of them.

As an officer, all that had changed. As his unhappiness increased, he became disinterested in his personal appearance and drank too much. Several months before admission the period of "acting-out" behavior began (cashing bad checks, running up debts, heavy consumption of alcohol), which resulted in his admission to hospital.

Background.—The patient was the second of three sons of an energetic father, who was 51 years old at the time of the patient's admission.

The eldest son had been an officer in the navy during World War II and had advanced rapidly to achieve moderately senior rank. He was now a successful businessman and a reserve naval officer.

The patient had always visualized the army as his career and had never thought of anything else since his earliest years. His childhood and adolescent phantasies had been associated with the army, with fighting, with a struggle for dominance, and with being a great and powerful hero. He had identified himself with heroes of history, mainly military figures.

The father was a youthful-looking, kindly but teasing, and very active man. A university graduate, he was successful in his profession. The patient and he had "wrestled together" well into adult life, and even recently on occasion. The patient described his father as "a great big man, even stronger than I." In point of fact, the patient was taller by an inch, and certainly broader and better built than his father. In their family great accent had been placed on "clean living, good athletic habits, and sports." The patient complained that when they wrestled now the father "still throws me."

The youngest son trained as an army officer while at university and was commissioned on graduation. As a result, though younger, he held

a higher senior rank than the patient. The patient was not consciously disturbed by this. The patient had only completed high school. Though academically gifted, he had refused to go to university and had immediately enlisted as a private in the regular army.

The mother was described as a retiring woman. Although the patient spontaneously spoke little of her, it soon became clear that the mother was a less kindly and more rejecting figure than the father. The father, by contrast, was seductive and warm, but at the same time overbearing and demanding, so that the patient felt that he could win his love only by adopting a passive and submissive attitude, at the same time identifying in part with a colder, harsher, rejecting, and therefore more powerful, woman figure. His ambivalence, hostility, and mixed identifications seemed to come from this need.

Behavior on Ward.—The patient was easy-going, affable, and superficially pleasant on the ward. He was very active in all sportive activities. Even with these outlets, he was restless and paced about, complaining that he felt "caged in." He often verbalized his need for "plenty of exercise and activity." He had an I. Q. of 130 on the Wechsler-Bellevue test.

In psychotherapy he showed a passive-dependent relationship with the doctor, wishing to please him and fearing his displeasure. He hid his underlying anxiety on this score with a great deal of surface affability. This anxiety was easily mobilized, and even superficial intrusion on sensitive areas, such as his family relationships, produced an increase in his restlessness, moodiness, and psychomotor activity. In the transference he showed strong dependency needs and the desire to be accepted. At the same time, he had to prove his independence and manhood by breaking ward rules in order to counteract and deny the dependency. Thus he consumed alcohol on the ward, returned late from pass, and continued to cash bad checks while in hospital. When not allowed on pass because of this behavior, he became increasingly anxious, paced and showed the beginnings of inappropriate euphoria. This euphoria alternated with moods of moderate despondency when his dependency needs or his desire for acceptance and recognition was frustrated, and underlying feelings of personal unworthiness became overtly apparent in these circumstances. When this occurred, his anxiety increased, and the need to act out, so as to "prove" his dominance, independence, and masculinity, would appear.

Superficially, he impressed people as extroverted and at ease with his environment. He gave this impression by sacrificing his own desires in order to be a generally pleasant and well-liked person. He felt much more at ease in the role of a subordinate, with well-defined tasks and limits. Any deviation from this produced considerable anxiety, despondency, and the acting out of his conflicts.

Because of the above-mentioned anxiety, despondency, and psychomotor activity, he was given reserpine, 2.5 mg. i. m., q. i. d. for 2 days, followed by 3 mg. orally q. i. d. for 11 days. His weight went from 210 to 218 lb. (94.5 to 98 kg.) in seven days, stabilizing at 218 lb. There was no edema. His appetite had been good, but on the drug the patient complained that he lost his "zest in eating." Blood pressure fell from 125/70 to 90/40 mm. Hg., depending on the dose, stabilizing in the vicinity of 100/60 mm. The pulse rate fell from 80 to 60 a minute (variation 80 to 56); the respiration rate remained at 20 a minute.

The patient felt that he was "worse." The "results in respect of affect" were considered "poor." The patient was slowed down; his motor activity was markedly cut; he was tired, drowsy, and irritable, and felt "held down." He could move his body, but tended to do so in one block, although he was able to do otherwise. He was unhappy, jittery, and extremely anxious. He felt cut off from life, "unable to sleep, unable to stay awake." He felt he was "going queer," that he was cut off "from outside things," and that his "body was changing."

The main observable changes were slowing down, inappropriate euphoria, panic at being chemically held, a feeling of change and dissociation and of changes in body image, and impairment of his motor control.

The "natural course of the disease" was "changed for the worse." From an acting-out person, who mastered his anxiety through activity, he became an inhibited, unhappy, frustrated man, whose mental content became psychotic, with marked suspiciousness about what was happening to him and of our motives, as well as a feeling of body-image changes. Nasal stuffiness was the only side-effect.

Because of his condition, the drug was discontinued, and the patient returned to his predrug state within a week. He was a very happy and relieved man about this, and remained with his acting-out behavior for the remaining month in hospital.

Comment

This case history is representative of this type of patient, and it is only the fact that reserpine removed his ability for vigorous motor activity at all levels that is significant. By so doing, it removed an outlet which represented a displacement of sexual energy into the sphere of activity.

This activity in the social sphere, and in his interpersonal relations, which had been libidinized ("sexualized") by displacement, (and thereby represented manhood or masculinity) was chemically removed. The libidinized activity had functioned as a denial of an underlying, feared, castrated state caused by strong feminine identifications.

The economy of the above equation (activity = masculinity, passivity = femininity) as an ego defense was chemically shattered. Regressed levels of ego defenses were thereby adopted, as shown by the body-image changes, paranoid distortions, etc.

Psychodynamics

The following common psychodynamic elements were found, and are illustrated in the 16 cases described.[12]

1. *Fear of Increased Passivity.*—A group of male patients, as in the case illustrated, with marked feminine identifications and passivity strivings (i. e., unconscious underlying needs to be passive, infantile, and cared for) and doubts about their masculinity, symbolically denied this fear and resorted to social, sexual, physical and/or intellectual activity as "proof" of their manhood. This activity meant being "masculine" and was a reassuring denial of many underlying identifications. Reserpine and chlorpromazine rendered a high level of muscular activity impossible. The patients were, as a result, rendered more passive. They were made tired and sleepy; they felt weak, and, above all, they were incapable of mobilizing formerly available energy into physical activity.

Here a series of activities representing displacements, and used by the ego as defenses to maintain better contact with reality, was, with dramatic suddenness, chemically removed or interfered with. The speed of the process is emphasized by its occurring in the space of minutes or a few hours, and with dramatic suddeness, thus not permitting time for adaptation. In short, a sudden and "brutal" * chemical interference with long-established modes of expression was produced, and the psychodynamic equilibrium of the equation (activity = masculinity, passivity = femininity) was suddenly ruptured. Repressed material was, as a result, brought closer to the surface, and either threatened to erupt into consciousness or did so. As a result of the threatened or actual break in the ego's capacity to handle this—fear, anxiety, projective, as well as autistic, thinking, with dissociation of thought processes, body-image changes, and increased depression were produced.

2. *Body-Change and Body-Image Group.*

Another group was considered as a subgroup of the above, but presented a different clinical symptomatology. These patients interpreted the multiple side-effects and physiological effects as a changing, or impairing, of their bodies. They sometimes developed body-image changes.

Others, usually with obsessive-compulsive neuroses and ruminating fears of impending bodily disasters, feared loss of control over their impulses and their bodies. The multiple unpleasant side-effects did impair mastery of their own bodies and resulted in a very real impairment of some organ systems, e. g., retching, vomiting, stuffy nose, diarrhea, dizziness, hypotension, dry mouth, hepatitis, etc. Such symptoms were very threatening to this type of patient. Here, again, repressed material was allowed to move closer to consciousness because some of the feared punishments and disasters for underlying guilt seemed to be personified by the action of the drugs. They responded with regression in their defenses; and symptoms of depersonalization, marked anxiety, a feeling of strangeness as to their own bodies, paranoid distortions, or increased depression resulted.

3. *Depressed Patients.*—Depressed patients became more depressed and anxious, as well as agitated and/or suicidal. The effects of the drugs in increasing psychomotor retardation, especially the motor aspects, reduced their already limited ability for interpersonal relations and, above all,

* This attitude on our part raises many questions as to countertransference.

for expressing aggression. This increased feelings of helplessness, worthlessness, and self-hatred.

4. *Drug as Assault or Seduction.*—A significant number of patients, including the only woman in the series, interpreted the effects of the drug as an assault, either heterosexual or homosexual. The marked and subjectively felt physiological effects of these powerful agents (in decreased activity, etc.) resulted in immediate suspicion, and in the patients distorting the physician's motives for reducing them to this state. Here, again, a poorer order of defenses had to be resorted in order to cope with this new situation, and anxiety, panic, and paranoid and dissociated thinking were produced.

Resulting Symptomatology

The psychiatric nosological entity produced was nonspecific as to drug, but was produced by the interaction of the pharmacological effects of the drug on the person's preexisting defenses, psychodynamic constellation, and the interpersonal, social, and reality factors facing him. Thus any variety of psychiatric nosological entity could theoretically result, and in this series the psychiatric symptomatology was quite varied.

Of the cases with a "good result on affect," 2 with the same physiological and psychodynamic constellations as some that did badly are reported, by way of contrast to the other 14.[12] Here, in the peculiar personal situation faced by these patients, the drug offered protection against a momentarily greater evil than the passivity, etc., it produced. In one patient with a homosexual panic, it offered unconscious symbolic gratification, in a safe hospital milieu, of the need to be homosexually assaulted, and thereby reduced this patient's anxiety. In the other, the threatened eruption of a murderous rage and hostility, which was directed both outwardly and against the patient himself, was rendered impossible by reducing the patient to a state in which he was barely able to move in bed, but was left with a clear sensorium (on a dose of 40 mg. of reserpine intramuscularly per day for 20 days). It was felt that, in other circumstances than these, these two patients would have been extremely threatened by the passivity, etc., imposed by the drug.

Conclusions

In this study, accidental (i.e., unforeseen and unplanned for) verification of psychoanalytic concepts of activity-passivity conflicts were obtained through the rapid chemical removal of means of expression used as major ego defenses. The patients' reactions to the very rapid interference with physical activity and self-control of their own bodies confirmed the data on activity-passivity conflicts in the male, long ago obtained by analysis of individual patients.[2,4-6,8]

Another, very important psychoanalytic concept demonstrated, by quick and drastic interference with patients' means of expressing themselves, was the concept of the continuum of ego defenses. Thus, when one series and means of maintaining contact with reality is interfered with, or is no longer available to the patient, a more dereistic or regressed (i.e., more disorganized, or "lower") group of defenses takes its place. The dramatic suddenness with which old means of dealing with problems and emotions were shattered or impaired threatened the hitherto used defenses against repressed material. This threatened emergence of repressed material produced anxiety.

When the chemical interference altered essential defenses, body-image changes, increased depression, depersonalization, dissociated and projected thinking, marked suspicion, and panic resulted. It is obvious that in the patients who are not the subjects of this communication (and who felt helped by the drugs), a reinforcing of their defenses became possible (as in the two patients cited who did well); and here again we see the continuum of ego defenses working in the upgrade direction (i.e., better-integrated defenses, or a "higher order").

The concept of an unbroken gradient or continuum of ego defenses, with better-organized ones giving way to less well-organized ones when they no longer sufficed to cope with anxiety [1,2,7,13] produced by conflict between repressed material and reality, was very amply demonstrated.

This paper is presented because in this study experimentation in psychiatry along lines of the more classic scientific method resulted in verification of long-established psychoanalytic conceptual models obtained through the classic psychoanalytic research technique of individual analysis of patients.

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Treatment of Chronic Schizophrenia with Promazine Hydrochloride

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Although a volume of literature concerned with the effects of tranquilizing drugs is accumulating, published reports of experimental or clinical trials with promazine hydrochloride are not numerous. Barsa and Kline [1] report a clinical effect similar to that found with chlorpromazine. Fazekas, Sullivan, and Schultz [2]; Mitchell [5]; Lemere,[4] and Usdin,[6] working mainly with a variety of acute psychiatric disorders, are in general agreement in reporting a positive clinical effectiveness of promazine therapy.

The following paper, the first of a series, discusses a study completed at Ypsilanti State Hospital in which an attempt was made to assess scientifically the effects of one of the newer phenothiazine derivatives, promazine hydrochloride, on various aspects of patient behavior and on blood pressure, blood count, and bone marrow.* This paper gives the experimental design for the study and includes a report of the effects of promazine on the behavioral adjustment of patients. Future papers will report the effects of promazine on attention, as measured by the reaction-time test, and on daily ward behavior, blood pressure, blood counts, and bone marrow.

The form of promazine hydrochloride (Sparine) used in the research is 10-(3-dimethylaminopropyl)-phenothiazine hydrochloride. Its structural formula is similar to that of chlorpromazine minus the chloride atom.

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* Promazine hydrochloride was supplied as Sparine by Wyeth Laboratories, Inc.

Experimental Design

Description of Patient Groups.—Ninety-three female patients with chronic schizophrenia, without regard to subtype, constituted the research population. The criterion for chronicity was a continuous period of hospitalization of at least five years. The patients ranged in age from 35 to 60 years, with two exceptions; one patient was 32 and another 61 years of age. All were considered to be of at least average intelligence (clinically determined). No patient in whom an organic pathology was primary was included in the study. Finally, no patient received any additional or adjunctive therapy during the course of the study. To arrive at the research population for the study, each patient was randomly assigned to one of three groups in a manner which assured equivalence of the groups with respect to scores obtained on a behavioral adjustment rating scale.

Table 1 summarizes age and length of hospitalization characteristics of the research populations. An examination of the Table shows that the different groups may be considered equivalent in composition. In addition, they are similar with respect to the distribution of the various subtypes (paranoid, hebephrenic, simple, catatonic, and undifferentiated).

The three equivalent groups were randomly assigned to one of three different treatment conditions—promazine, placebo, no treatment. The procedure thus far followed resulted in the traditional before-after design (designated the basic design in the present study) with two control groups, one receiving a placebo, and the other nothing, and one experimental group receiving promazine. Changes in behavior as a function of time, ward conditions, and the psychological effect of receiving medication were thus controlled, leading to a more accurate measurement of the effects of the drug.

The research design was further extended and refined to permit a more rigorous assessment and evaluation of promazine therapy. The extension was achieved by splitting each of the three original groups into two groups, again equating for ranks on the behavioral rating scale. This resulted in six matched groups, each subjected to a different

TABLE 1.—*Mean Age, Age Range, Mean Years in Hospital, and Range of Years in Hospital for All Groups in Study Design*

Group	No.	Mean Years of Hospitalization	Range, in Years, of Hospitalization	Mean Age, Yr.	Age Range, Yr.
I	31	*19.5*	*5-35*	*49.5*	*35-60*
A	16	14.1	5-25	52.3	39-60
B	15	12.1	5-24	46.3	35-60
II	31	*19.0*	*5-33*	*50.6*	*37-60*
C	16	13.0	5-23	51.3	39-58
D	15	13.9	7-23	9.9	37-60
III	31	*11.7*	*5-26*	*49.4*	*32-61*
E	16	13.2	5-23	49.7	32-61
F	15	10.1	5-25	49.1	39-60

treatment schedule. The splitting procedure could have been carried out further, but statistical and logical considerations dictated against further reduction of the number of cases within each schedule. The research designs, referred to as Basic and Extended, are shown in Table 2. It will be noted that each treatment schedule lasted one month, or, more specifically, 28 days.

The Behavioral Adjustment Scale.—The Gardner Behavior Chart was the instrument used to measure behavioral adjustment at various points in this study.[7] It is a practical and useful instrument for evaluating behavior. The information it utilizes is both direct and concrete, contributing to its inherent or face validity. The structure of the chart is such as to minimize the possibility of misconception and misomprehension on the part of the hospital personnel (in this instance, attendants) supplying the information. Adjustment levels for the following behavioral categories are rated: attention to personal appearance, sleep patterns, appetite, sociability, activity control, noise disturbance control, temper control, combativeness control, care of property, self-entertainment, cooperation in routine, work capacity, work initiative when alone, work initiative when supervised, and willingness to follow directions.

Under each of the 15 categories, five brief phrases characterize the degree or level of adjustment. The quantitative evaluation is obtained by assigning a numerical value of 0 to 4 to each of the five descriptive phrases. Attendants who were responsible for completing the scales were given training prior to the start of the study. The degree to which attendant-raters agreed in their evaluation of patients' level of behavior adjustment in the present study was estimated by the Spearman rank-difference coefficient of correlation method. Table 3 shows that, with the exception of Raters A and B, the various pairs of raters were in very high agreement in their evaluations of patient behavior. The obvious reduction in the coefficient for Raters A and B cannot be fully explained. On the whole, the results suggest that the training schedule to which the raters were subjected was successful in preparing them for their task, and behavioral measures obtained throughout the study are considered to be both reliable and stable, lending themselves to comparison at various points in the study.

Experimental Procedure.—The double-blind technique was employed throughout the study. Patients received their medication (drug or placebo) in individual, sealed envelopes. Neither the patient nor the attendant dispensing the envelopes was

TABLE 2.—*The Experimental Design: Treatment Administered to Each Group by Month*

Group*	N	Basic Design	Extended Design		
		First Month	Second Month	Third Month	Fourth Month
I A	16	Drug	No treatment	Drug	No treatment
I B	15		No treatment	Placebo	No treatment
II C	16	Placebo	No treatment	Drug	No treatment
II D	15		No treatment	Placebo	No treatment
III E	16	No treatment	Drug	Drug	No treatment
III F	15		Placebo	Drug	No treatment

* Groups I, II, and III refer to groups in the basic design.

TABLE 3.—*Interrater Reliability Coefficients on the Gardner Behavior Chart*
Spearman's Rank-Difference Method

	Rater		
Rater	A	B	C
B	<0.545 *P*0.02	—	—
C	0.809 *P*<0.001	0.926 *P*<0.001	—
D	0.894 *P*<0.001	0.755 *P*<0.001	0.769 *P*<0.001

cognizant of the kind and amount of medication contained in each envelope. Those attendants who rated the patients' behavioral adjustment did not dispense medication and were unaware of the experimental group to which a patient was assigned.

In addition to a prestudy measure, adjustment ratings were obtained on the seventh and last day of each month of the study. It was possible, with these nine ratings, to determine the effects of promazine and changes in the treatment schedule at differing time periods.

The complete medication schedule will appear in future papers reporting on laboratory findings. The present discussion is limited to the first month of the study—the basic design. The drug was administered orally, in capsule form, four times daily. All patients were started on a daily total dose of 150 mg. On the third day this amount was increased to 300 mg. and on the sixth to 600 mg. On the 15th day the dose was increased or decreased, depending on the requirements and tolerance level of each patient, as determined by the clinical impression of the attending psychiatrist. Most patients were maintained on 900 mg., increasing to 1200 mg. on the third day. The dose required for maintenance after and including the 15th day ranged from 400 to 1400 mg. Placebo administration to each patient in Group II corresponded identically with promazine medication to the matched patient in Group I. The pharmacologically inactive placebo was in every respect similar to the drug in appearance. On very rare occasions it was necessary to depart slightly from the above schedule with individual patients. These modifications, however, were not considered to be important to the extent of altering the over-all outcome.

Results

Statistical Procedure.—The statistical procedures described were applied to the quantitative ratings on the Gardner Behavior Chart, previously discussed.

A complete ranked one-way analysis of variance was done separately for all comparisons made both among and within groups in the experimental design. This method, developed by Kruskal and Wallis,[3] is referred to as the H-test and tests the hypothesis that the groups are similar or that there are no differences. The use of this statistic in the analysis of the Gardner Behavior Chart data was based on a consideration of the extent to which the data met the assumptions and requirements necessary for the appropriate utilization of classical statistical techniques. The structure of the Chart, the conditions under which the data were obtained, and the manner by which the Chart is scored, all contribute to the necessity of a conservative approach to interpretation. The only two assumptions which were readily acceptable were that the variable under investigation was a continuous one and that all groups were treated similarly except for the experimental conditions. The proper use of the H-test is not dependent upon assumptions of normality or homogeneity of variances. In addition, the H-test is not affected by whether or not the items in the Chart have equal weights, or by whether or not the items are scored on an equidistant interval scale. Finally, variation between raters in no way weakens the interpretation of the obtained H values.

Changes in Patient Behavior—Basic Design.—As measured by the H-test, the behavioral adjustment changes occurring within each group taken separately are not statistically significant. It is to be observed in reading the Tables that low scores represent high ranks, and, therefore, a greater level of adjustment. The probabilities (*P*) shown in Table 4, indicate that changes which did occur within groups can be expected on the basis of chance alone. None of the three therapeutic approaches, therefore, is considered to have a significant effect on the level of behavioral adjustment as measured by the Gardner Behavior Chart. More specifically, the effect of promazine as a pharmacodynamic agent in the treatment of the class of patients utilized in this

TABLE 4.—*Changes in Mean Ranks on the Gardner Behavior Chart*
H-Test, Complete One-Way Ranked Analysis of Variance

Group		Mean Ranks			Within Groups	
		Pretest	After 7 Days	After 28 Days	H *	*P*
I Promazine		46.74	42.87	45.35	1.02	>0.50
II Placebo		47.45	50.00	48.35	1.38	0.50
III No treatment		46.87	45.32	47.35	0.27	>0.80
Between groups	H *	0.27	10.00	0.46		
	P	>0.80	>0.001	>0.80		

* All values of H have been corrected for ties.

study was similar to that found with a placebo or with no treatment.

Differences among groups show a statistically significant difference (*P* among groups) after 7 days, but not after 28 days. At the seven-day point, the separation between the adjustment levels of the promazine and placebo groups accounts for the obtained difference. This results from improvement in the promazine group, accompanied by a loss in the placebo group. The trend in these two groups was reversed after the 7th day, resulting in similar levels of adjustment on the 28th day. The similarity of the three groups on pretest measures is expected, of course, as a result of the matching procedure.

The effect of regular versus irregular promazine medication on behavior adjustment was investigated by dividing Group I (promazine group) into two groups, of 11 and 20 patients each. In the 11-patient group, promazine medication followed a schedule of progressively increasing doses at regular intervals. In the 20-patient group, the medication schedule was characterized by both increased and decreased doses at irregular intervals.

TABLE 5.—*Differences Among Groups on Regular and Irregular Drug, Placebo, and No-Treatment Schedules*
H-Test, Complete One-Way Ranked Analysis of Variance

Group *	Mean Ranks After 28 Days	No. of Patients
I Regular drug schedule	41.73	11
I Irregular drug schedule	47.30	20
II Placebo	48.35	31
III No treatment	47.35	31
H †	0.50	
P	>0.90	

* Groups were matched and equated at beginning of treatment.
† All values of H have been corrected for ties.

Table 5 shows that no differential effects at a statistically significant level were found when patterns of medication schedule were taken into account. Only conclusions based on measurements taken on the 28th day are presented, since differentiation of medication patterns was not possible up to the 7th day of treatment.

Changes in Patient Behavior—Extended Design.—At no point in the study did differences among or within the six groups in the extended design reach statistical significance. The influences of the various experimental conditions, it can be concluded, were not such as significantly to separate any single group from the others, in terms of behavioral adjustment as rated by trained attendant-raters using the Gardner Behavior Chart. Changes did take place, as a study of Table 6 will show. But these changes can well be considered due to chance and sampling factors, and not due to the effects of the treatment programs.

Comment

The failure to obtain evidence of improvement in behavior, though contrary to the majority of published reports, is in agreement with results obtained by employing similar constructed rating scales in assessing the effects of ataractic drugs. The contrary results found in many published reports

TABLE 6—*Differences in Mean Ranks on the Gardner Behavior Chart Among Groups and Between Highest and Lowest Ranks Within Groups*
H-Test, Complete One-Way Ranked Analysis of Variance

Group	Prestudy	Mean Ranks on the Gardner Behavior Chart								Within Groups H *†
		First Month		Second Month		Third Month		Fourth Month		
		7th Day	28th Day	35th Day	56th Day	63rd Day	84th Day	91st Day	112th Day	
A	46.93	43.75	43.19	42.38	44.31	41.31	41.62	43.62	41.81	1.30
B	46.53	41.93	47.67	49.87	47.13	49.13	48.00	46.26	45.73	0.37
C	46.81	49.44	49.94	50.69	52.62	55.87	50.93	51.12	56.31	0.02
D	48.13	50.60	46.67	47.73	45.26	48.00	53.13	52.66	49.67	0.79
E	46.13	46.44	47.56	45.88	47.25	44.93	44.93	44.75	46.31	1.11
F	47.67	44.13	47.13	45.67	45.06	42.73	43.73	43.80	41.80	2.75
H †‡ Between Groups	0.32	9.90	0.79	1.14	0.74	3.15	2.34	1.87	3.40	

* H required for $P0.05=3.84$ with 1 d.f.
† All values of H have been corrected for ties.
‡ H required for $P0.05=11.07$ with 5 d.f.

may well be due to failure to utilize objective procedures, or it is quite possible that factors which were not controlled in these studies may have been primarily responsible for any improvement noted rather than that the medication per se was effective. On the other hand, in this study, the failure to find significant behavioral changes with drug therapy may be due to several factors. Amount, route, and frequency of dosage and the length of time over which the patient is treated, aspects which will be discussed at length in papers to follow, may all have some bearing on the obtained results. It is possible that the schedules adopted for this study were such as to preclude improvement in the clinical material treated. The degree of chronicity in these patients might well be too severe to result in a generalized therapeutic effect following the use of promazine. The absence of improvement, either among or within the six groups, strongly points to an over-all ineffectiveness of promazine in the treatment of severely chronic schizophrenic female patients. On the other hand, results with acute disorders, as reported in the literature, have been most encouraging. These findings may well reinforce suggestions that selection of particular and specific clinical material for treatment with promazine is necessary and further support the impression that promazine has a differential effect on patients presenting different kinds of psychiatric disorders.

Evidence of behavioral changes due to increased attention to patients, changes in general ward atmosphere produced by the research project, suggestion, more patient-staff contacts, and placebo effects was absent in the present study. Many other studies have reported a positive effect from these and other factors. Failure to find confirming results in this study could be due to the control exercised in conducting the research or to a lack of influence on the part of patients with drug improvement (which did not occur) on patients treated without drugs.

Summary

Ninety-three female chronic schizophrenic patients were divided into three matched groups, each of which was subjected to a different treatment schedule—promazine, placebo, no-treatment (basic design)—for a period of 28 days. The basic design was extended to form six matched groups, each subjected to a different treatment schedule employing promazine hydrochloride (Sparine). The total experiment was conducted over a period of four months. Nine measures of adjustment were obtained, using the Gardner Behavior Chart. In addition to a prestudy measure, ratings were made on

the 7th and 28th days of each of the four consecutive months over which the study was conducted. The effects of regular and irregular drug schedules are also presented and discussed. It is stated that future papers will present and discuss results obtained on studies of attention, ward behavior, blood pressure, blood counts, and bone marrow.

Conclusions

Changes in behavioral adjustment of female chronic schizophrenic patients produced by administration of promazine failed to attain statistical significance. In general, it can be concluded that there were no behavioral changes occurring in any group of patients which could be associated with administration of promazine or a placebo or with no treatment.

No difference between regular and irregular patterns of administering medication with regard to amount and frequency of dosage was obtained.

It is felt that, while no changes in behavior adjustment were obtained from using promazine in what is considered an adequate test of its effectiveness, further research should be directed toward the development of procedures and techniques that might identify specific clinical characteristics which respond positively or are refractory to promazine therapy.

The present findings can in no way be used to anticipate results obtained in other areas of behavior investigated in this study, and which will be reported and discussed in later papers.

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Visual Discrimination and the Decision Process in Anxiety

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This paper deals with the relationship between anxiety and perceptual functioning, studied as part of a larger investigation of concomitant variations among several selected aspects of affective, psychological, and physiological functioning under the impact of experimentally induced anxiety. Here we shall be concerned principally with the changes in perceptual behavior, measured in the accuracy and speed of visual discrimination, over a number of days during which anxiety-prone patients were subjected to anxiety-provoking interviews. The theoretical and methodological rationale of the larger study, and the details of the experimental design and of other variables studied have been described elsewhere.[1]

The basic experiment covered a four-day period. On the first of these days, anxiety-prone and anxious subjects, selected from the patients of a psychiatric hospital, were brought to the laboratory and given each of the test procedures. This day (the pre-experimental day) was designed to accustom subjects to the laboratory and to test equipment and procedures. The focal point of each of the three following experimental days was a stress interview, originally intended to be intensified from day to day, which was preceded and followed by the same series of experimental measures (pre- and postperiods). The four-day design, as originally conceived, could permit evaluation, within the same subjects, of the extent of stress responses and the relations among the various indicators as the level of stimulation is increased, at the same time providing a basis for assaying the variability of response and the temporal trends over the four-day period.

The stress interviewer attempted to increase anxiety in a quasipsychiatric interview by his revelation and interpretation of conflictful material and his attitudes expressed toward the subject and his manipulation of communication, adjusting his behavior in each case on the basis of previously obtained knowledge of the patient's personality and crucial areas. The final effectiveness of the stress interview depended, however, on the actual interviewer-patient transactions, which were determined in the particular case by the feelings, expectations, and role perceptions of each participant and often reflected influences from the larger social setting in which the experiment was conducted. Consequently, intended actions often led to unpredictable, and sometimes paradoxical, results. A detailed analysis of the interview procedure and the factors which determine its anxiety-producing value is presented elsewhere.[2] For our present purpose it is sufficient to note that, while

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the interview did in general increase emotional disturbance, as rated by observers, a graded series of anxiety increments could not be achieved.

By the nature of the over-all experimental design all of the test procedures used had to meet a number of requirements. They should be (1) short, in order that a number of tests could be fitted within the pre- and postperiods; (2) repeatable, without earlier testing affecting subsequent performance; (3) noninteractive, i. e., minimally interfering with each other, either in terms of the mechanical requirements of testing or, more importantly, by directly inducing changes in the subject and (4) minimally productive of anxiety themselves.

As an index of psychological functioning to be related to stress-induced emotional changes and to other measured variables, a visual perceptual procedure was developed in which subjects had to decide which of two simultaneously viewed squares was larger. Performance on this Area Judgment Test was evaluated for two separable aspects of perceptual decision making—the accuracy of the discriminations and the time required for decision, both of which were expected to vary in anxiety. To describe the effects of anxiety, these studies will be considered in terms of four related issues: (1) the changes in the patterns of performance of anxious patients through repeated occasions of testing; (2) the specific effects of the experimental stress; (3) the relation between performance and emotional levels, independently assessed, and (4) the contrast between anxious patients and nonhospitalized, normal controls. For the last-mentioned purpose, supplementary studies were done outside the major experiment.

Subjects and Procedure

The main experimental group consisted of 19 subjects, all but one from the inpatient population of the psychiatric institute of a general hospital. Thirteen were men and six women. The mean age of the group was 39 years, with a range from 22 to 57 years. A patient was included either if interview and examination of clinical records revealed free anxiety as an important part of his current symptom picture or if it could be judged from his history that he would be prone to develop anxiety under stress. Various diagnostic entities were represented, though "anxiety state," "agitated depression," and "borderline character disorder" were the most commonly recorded diagnoses. Since the experimental design requires a considerable degree of cooperativeness and the restriction of activity during the several hours in the laboratory, markedly anxious, agitated patients could not be included. Similarly, there were no overtly psychotic patients in the group. Both the patients and their attending psychiatrists voluntarily agreed to their participation in the study, with some hope that the results of the various tests might be useful in subsequent treatment, although the specific procedures and purposes of the experiment were not explained to the patients.

As a nonpatient, control group, 18 normals were recruited from among the white-collar, nonmedical personnel of the general hospital. The group was so chosen as to be similar to the patients in age and sex and roughly comparable in educational level. This group consisted of 12 men and 6 women. Their mean age was 41 years, ranging from 25 to 60 years. The control normals were given the Area Judgment Test twice, exactly 24 hours apart, in the same laboratory room used for the patients. However, they did not undergo any of the other test procedures, nor were they given the stress interview. Although the control group had fewer occasions of repeated testing than the patients, testing twice allowed not only for the comparison of the groups in terms of the level of performance on each occasion but also of the change between the two. The normals' two trials were spaced like the first two occasions on which the patients were tested—preexperimental day and preperiod of Day 1—both of which preceded the first stress interview.

In the Area Judgment Test subjects were asked to judge which of two squares shown simultaneously was larger. The squares used were 36, 37, 38, and 39 mm. on a side. The test consisted of 45 pairings, in 15 of which the sides of the two members differed by 1 mm., in 15 by 2 mm., and in 15 by 3 mm. The test stimuli varied as well on a number of irrelevant factors, included solely to increase complexity and difficulty of discrimination. These were (1) color—each square could be red, green, blue, or yellow—(2) angular position—each square could be aligned parallel to the horizontal and vertical edges of the card or rotated 45 degrees—(3) distance—the two squares could be relatively close (1 in.) or farther apart (4 in.)—and (4) location—a square could be aligned on the same or a different horizontal or vertical axis as its

comparison figure. The squares were paired randomly with respect to these factors and mounted on separate white cards. For each trial the cards were presented in a different random order. During testing the experimental room was darkened and the cards exposed in the viewing box of a Gerbrand tachistoscope, ensuring even illumination over the visual field. Instructions given prior to each trial were essentially these: "I am going to show you two figures, and I want you to compare their sizes. If they are different in size, I want you to tell me which one is larger. If they seem to be the same in size, or you can't tell the difference, say 'Same.' Before I show you each card, I am going to say the word 'ready,' which will tell you that the figures will appear shortly." When the test field was illuminated a 0.01-second timer was activated, which was stopped when the subject responded. Subjects were never told whether they were correct, either after the single judgment or after the entire series. Responses were scored for both accuracy and decision time.

Results

Differences in Performance Between Experimental Occasions.—Over-all, patients varied considerably in performance. Taking all patients on all occasions of testing, the over-all mean accuracy score (number of correct judgments to the 45 items) was 34.2, and the mean decision time was 2.91 seconds per judgment. However, the range of individual mean accuracy scores ran from 19.7 to 42.7, while in their speed of decision the quickest subject averaged 1.75 seconds and the slowest 5.33 seconds. In the main, the errors that were made consisted of not discriminating between the two stimulus squares—calling them "same"—and only infrequently did a subject describe the smaller square as larger. Although the frequency of error differed among subject groups and test occasions, the type of error made remained quite constant.

The effects of the stress interview are seen in most general form in Table 1. It is striking that over-all there is relatively little change in either accuracy or decision-time values between the seven occasions of measurement. In accuracy, the level rises slightly from before to after the stress on the first experimental day and falls somewhat from before to after stress on Day 2 and Day 3. Only on Day 2 is the drop significant (on one-tailed test, $t=3.462$; $P<0.005$). The changes between occasions may be viewed in still another manner, which gives further evidence of the stress effects. If we consider the number of subjects who change in each direction from pre- to poststress on each experimental day, it is found that 11 of the 19 improve on Day 1, whereas 2 remain the same and 6 decline. On Day 2, however, only 3 improve; 2 remain the same, and 14 become worse. On Day 3, 4 improve; 3 remain the same, and 12 decline in accuracy. Thus, it would seem that, however small the mean changes, there is a distinct tendency for the stress on Days 2 and 3 to reduce the adequacy of judgment.

Interestingly, there is little evidence of any over-all trend in the group's performance. The preexperimental day level is as high as any single occasion during the remainder of the experimental week. As in much repeated testing, it might have been anticipated that either because of learning or because of acclimation in the situation there would be some degree of improvement from the preexperimental day to later occasions. Yet, rather little change is found.

Although there is more change in decision time from the preexperimental day to later occasions, the level thereafter tends to re-

TABLE 1.—*Mean Accuracy and Decision-Time Values on Each Occasion* (Anxiety Patients, N-19)

	Preexperimental Day	Day 1*		Day 2		Day 3	
		Pre-	Post-	Pre-	Post-	Pre-	Post-
Accuracy, no. correct	34.9	32.7	33.9	35.6	32.8	35.0	33.9
Decision time, sec.	3.45	2.88	2.54	2.77	2.70	2.76	2.82

*Pre- and poststress values.

main stable. Subjects are slower in their first contact with the task, though no less accurate. None of the pre- to postperiod changes on any experimental day even approaches significance.

In general, then, the effects of this experimental stress are not great on this test. On two of the days there is the anticipated drop in accuracy, which is, however, small. There is no consistency for the decision-time values for the group as a whole.

Difference in Performance on Days Varying in Affective Response.—Although most subjects showed differences in the amount of emotional response to the interview stresses of the three experimental days, the intended increment from day to day was by no means the general case.[2] Consequently, grouping all subjects' data for each of the experimental days combines varying degrees of stress response. We can reconsider the already presented perceptual data, regrouped, however, in terms of stress intensity, as defined by observed rather than by intended emotional change. Thus, to explore further the relationship between emotional state and perceptual performance, "stress" is considered here in terms of the amount of affect evoked.

Three artificial "days" were created: the day of greatest emotional response, the day of least emotional response, and the day of median emotional response. For all subjects, the pre- to poststress change in Area Judgment Test scores were combined for these "high," "median," and "low" days, defined by the pre- and poststress changes in the affective level, as rated by observers. It should be noted that for one subject the "high" day may actually have involved a sizable increase in affect and his "low" day no change or a smaller rise; for another, the "high" was actually no rise, the "low," a sizable drop. Hence "high," "median," and "low" day has meaning only in terms of the relative range of affective change within each subject. However, the procedure does ensure maximal separation of the stress occasions, in affect terms, within what is generally a limited range of emotional response.

This analysis was performed for each of the three affects separately rated—anxiety, anger, and depression—and for the simple sum of the three combined. This last provides a measure, though crude, of the general amount of "emotional disturbance" aroused by the stress interview, which the former three ratings attempt to differentiate into major components.

The mean accuracy and decision-time values for the "high," "median," and "low" days for each of the four affective ratings are shown in Table 2. Although in all comparisons the differences among affect-days in mean accuracy scores are not great, and often fall short of statistical significance, the over-all picture is clear. Generally, the greatest drop in subjects' accuracy scores occurs when the greatest amount of affect was observed; the least, on the occasions of smallest affect increase. The largest differences are found when the data are grouped by anger ratings and by the combined affect. For anger, the difference between the highest and the lowest day is significant at the $P<0.01$ level ($t=2.715$), between the median and the lowest day at the $P<0.005$ level ($t=3.432$). Similarly, both the differences between highest and lowest and median and lowest combined-

TABLE 2.—*Mean Pre- to Poststress Change* in Accuracy and Decision-Time Values on Days of Highest, Median, and Lowest Increase in Each Affect*
(Anxious Patients, N-18)

	Anxiety			Anger			Depression			Combined Affects		
	H	M	L	H	M	L	H	M	L	H	M	L
Accuracy	−2.11	−1.83	−0.11	−2.44	−2.39	+0.78	−1.67	−1.67	−0.72	−2.72	−2.00	+0.67
Decision time	−0.02	−0.31	−0.14	−0.25	−0.14	−0.08	−0.29	+0.03	−0.21	−0.22	−0.09	−0.16

* Calculated as post-minus prestress; hence positive value indicates increase.

affect days are significant at the $P<0.01$ level ($t=2.704$ and 2.778, respectively). In every comparison, however, the drop in accuracy decreases from "high" to "median" to "low" day.

By contrast, the mean decision-time values show little regularity when compared by days of differing affective response. The differences are small and insignificant, and there is no indication of trend.

Correlations Between Test Performance and Emotional Levels.—Are there direct correlations between emotional levels and performance on the Area Judgment Test, over-all or, more specifically, in response to the stress on each of the experimental days?

At the grossest level, the individual mean accuracy and decision-time scores were correlated with the mean ratings of each of the affects, for all of the periods of the experiment combined. There is no indication of any significant correlation between the over-all levels of any of the rated affects and either of the perceptual measures. For the mean accuracy scores across the four days of the experiment the following correlations (r) are found: with anxiety, +0.114; with anger, −0.018; with depression, +0.049, and with the combined affect ratings, +0.244. Similarly, mean decision-time scores correlated as follows: with anxiety, −0.103; with anger, −0.309; with depression, +0.105, and with the combined affect ratings, −0.195. These analyses make it perfectly clear that there is no consistent relationship between the perceptual measures and any of the rated affects when each is considered in terms of individual subjects' over-all levels over the various occasions of the experiment.

If the emotional ratings and test scores are compared in terms of the pre- to post-period (stress-induced) changes within each of the experimental days separately, somewhat more relationship between affect and perceptual performance emerges (Table 3). The correlations in Table 3 are based on the pre- minus poststress change scores for each subject in each variable; hence positive correlation would indicate coordinate increase in both variables from before to after the stress interview.

TABLE 3.—*Correlations (r) in Pre- Minus Poststress Values Between Accuracy and Decision Time and Each of the Rated Affects on Each of the Experimental Days*
(Anxious Patients)

Affect	Day	Correlation with Accuracy	Correlation with Decision Time
Anxiety	1	0.319	0.304
	2	−0.310	−0.153
	3	−0.558 *	0.487*
Anger	1	0.033	0.440†
	2	−0.606 ‡	0.003
	3	−0.369	0.139
Depression	1	0.200	0.114
	2	0.013	−0.440†
	3	−0.301	0.393†
Combined affect	1	0.197	0.369
	2	−0.319	−0.283
	3	−0.526*	0.445*

* Significant at $P<0.05$ level.
† Significant at $P<0.10$ level.
‡ Significant at $P<0.01$ level.

Although relatively few of the correlations reach acceptable levels of reliability, there do appear to be trends between experimental days in terms of the extent and direction of correlation. For the accuracy scores, on the first experimental day correlations tend to be low and insignificant, but positive. During the last two days, though the correlations are still low, there is somewhat more relationship, and more important, the coefficients tend to become negative. Thus, on the first day those subjects who are judged to become more anxious tended to do *better* on the perceptual task ($r=+0.319$), but by the third day the relationship reverses and the more anxious subjects perform *worse* ($r=-0.558$). Although this trend from positive to negative correlation is found for all four sets of affective ratings, there are visible differences in amount. Notable is the correlation with anger on Day 2, which is the highest achieved in any of the comparisons ($r=-0.606$). Interestingly, the second experimental day was characterized by the greatest increases in anger following the stress interview.

Although the correlations between affect changes and decision-time changes are no lower than those for accuracy, there is less

indication of any regular trend from Day 1 to Day 2 to Day 3 (Table 3). Generally, the correlations are positive and tend to be higher on the third day; the only three negative correlations are all obtained on the second day.

Since the three major affective ratings tend themselves to be distinctly correlated, and because of the generally low levels of correlation throughout this analysis, any speculation about the specific patterns of perception-affect relations is certainly not warranted. However, the over-all conclusion that the stress-induced changes in affect-in-general and in the perceptual variables studied are related, but that the nature of the relationship changes from day to day may be justified. On the first day, noted before as the only day of over-all improvement in accuracy, increase in emotional disturbance is paralleled by more accurate and somewhat slower performance; on the second day, by decrease in accuracy and speeding of response; and on the last day, by both decreased accuracy and slowing of response.

Comparison of Anxious and Normal Subjects.—In order to understand better the data obtained for the anxious patients in the larger experiment, we may contrast some aspects of their performance with those of the psychologically healthier employee group. As we described earlier, control subjects were tested on two occasions, at the same hour on consecutive days and in the same laboratory setting as the patients. Unlike the patients, the Area Judgment Test was the only procedure administered; the other tests and the stress interview were not included. However, the normals' two occasions can be likened roughly to the patients' preexperimental day and the preperiod of Day 1, the patient's first and second occasion of testing both prior to the first stress interview. Thus, patients and normals can be compared in their levels of functioning and in certain within-test patterns, on each occasion and in terms of the change between occasions. Our concern here is with whether there are regular differences in performance which may characterize anxious persons regardless of their already noted behavior in the stress experiment.

For this analysis two subjects in the patient group were not included. One of these was not tested on the preexperimental day, and the other could not be tested on the first session of Day 1. Thus, the number of subjects in the patient group is 17; in the normal, 18.

The mean accuracy and decision-time scores for each of the groups are given in Table 4. The column labeled "decision time (total)" contains the mean values for all items. In addition, the decision times for correct and incorrect judgments are given separately in the last two columns. These will be discussed later.

When the accuracy scores are viewed, two findings quickly emerge: (1) The groups are quite similar; if anything, the patients perform a bit better. (2) Performances on the two occasions differ little. The slight differences between groups and between occasions are insignificant. By contrast, there is relatively more difference between groups and between occasions in the decision-time values. The patients require longer time to make their judgments on both trials; the difference approaches the $P=0.10$ level on the second day ($t=1.68$), though falling somewhat short on

TABLE 4.—*Mean Accuracy and Decision-Time Values on Two Occasions of Testing* (Anxious Patients, N-17; Normals, N-18)

Group	Occasion	Accuracy	Decision Time (Total)	Decision Time (Correct)	Decision Time (Incorrect)
Patients	1	35.5	3.38	3.21	4.44
	2	34.5	2.78	2.61	3.87
Normals	1	33.2	2.71	2.70	2.80
	2	32.0	2.23	2.18	2.60

TABLE 5.—*Mean Accuracy and Decision-Time Values on Two Occasions of Testing, by Stimulus Difference*
(Anxious Patients, N-17; Normals, N-18)

Group	Occasion	Accuracy (No. Correct)			Decision Time (Seconds)		
		1 Mm.	2 Mm.	3 Mm.	1 Mm.	2 Mm.	3 Mm.
Patients	1	8.35	12.47	14.65	3.93	3.60	2.65
	2	8.24	11.88	14.41	3.26	2.78	2.31
Normals	1	8.00	11.56	13.67	3.04	2.74	2.34
	2	7.50	11.17	13.33	2.40	2.28	2.02

the first day ($t=1.54$). However, compared with their first trial, both groups become significantly faster on the second day (patients, $t=3.15$, $P<0.01$; normals, $t=3.10$, $P<0.01$).

The groups differ rather interestingly in their decision times on correct and incorrect items (Table 4). Since the accuracy scores are almost identical, these values are based on approximately the same number of correct and incorrect judgments for each subject group. The normals do not take substantially more time in making incorrect than correct judgments. The patients, by contrast, are distinctly slower when making judgments which are wrong. Comparing the two groups in terms of the difference between decision times for the correct and the incorrect items, it is found that the mean difference is significantly larger for the patients on the first occasion ($t=2.30$, $P<0.05$), and in the same direction, though short of statistical significance, on the second occasion ($t=1.35$). Stated otherwise, the patients and the normals are much more alike when correct, much more distinct when incorrect. If one considers decision time a measure of the conflict in the judgmental situation,[3,4] it would seem from these data that the anxious groups are more in conflict generally and decidedly more so when they cannot discriminate the stimuli.

Accuracy and Decision Time as a Function of Stimulus Differences.—The Area Judgment Test, it will be recalled, requires the discrimination of stimulus-pairs, which differ by 1, 2, or 3 mm. on a side. One should expect that subjects should be both more accurate and faster in their decisions as the difference in size between the com-

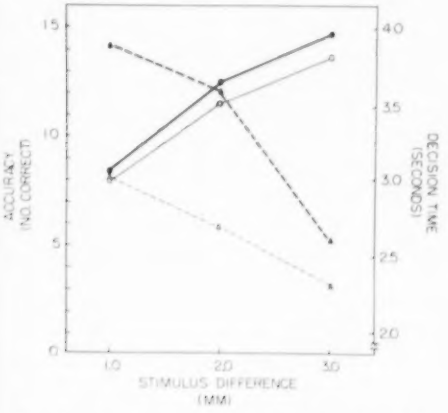

Fig. 1.—Accuracy and speed as a function of the differences in size of the stimulus pairs for the first test occasion. Accuracy values are connected by solid lines, and decision time, by dashed lines; curves for patients are heavily drawn, and those for normals, lightly drawn.

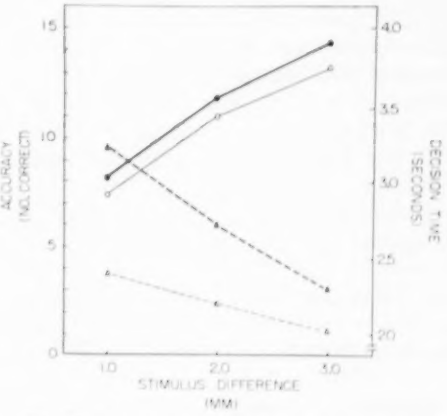

Fig. 2.—Accuracy and speed as a function of the differences in size of the stimulus pairs for the second test occasion. Accuracy values are connected by solid lines, and decision time, by dashed lines; curves for patients are heavily drawn, and those for normals, lightly drawn.

parison stimuli increases. The possibility of error decreases and the certainty of judgment increases as the discrimination becomes objectively easier.

The mean number of correct judgments and the mean decision times for the 15 items at each of the stimulus-difference levels are given in Table 5 and plotted in Figure 1 for the first trial and in Figure 2 for the second trial. As the difference between stimuli increases, there is a clear rise in accuracy and coordinately a fall in decision time. This pattern is basically the same in the two groups and on both occasions of measurement. Moreover, the group differences already noted in total scores hold equally for the subgroups of items: The patients are somewhat more accurate, and they are slower in their decision times for each of the three sets of items, as they are in the total for all 45 items combined (cf. Table 4).

However, while the curves for accuracy values (Figs. 1 and 2) are virtually parallel, there tends to be some convergence in the decision-time curves. The patients and normals are most distinctly different for the 1 mm. items, least so for the 3 mm. items. It would appear, then, that the more difficult the judgment, the proportionately slower the patients are as compared with the normals. As both groups adjust to the task, Trial 2, both the absolute and relative differences between them decrease, but even on the second occasion the groups are more distinctly separated in the time taken to judge the more difficult than to judge the simpler items.

It may be remarked that these findings on decision time as a function of stimulus-differences might duplicate the already noted findings that patients are slower when making erroneous judgments, since most of the errors are made with the 1 mm. pairs and increasingly fewer with the 2 and the 3 mm. pairs. However, if the times for correct and incorrect items are separated within each of the stimulus-difference groups (Table 6), generally the patients show proportionately slower times for incorrect than for correct judgments. This is particularly true on the first occasion, where the significant difference in over-all mean times has already been seen, and less so on the second occasion, with its relatively smaller over-all differences. Generally, then, the patients seem to have greater difficulty in resolving the judgmental conflict when objectively the discriminanda are minimally different and have particular difficulty in reaching or admitting the decision that there is no discernible difference between a pair of stimuli ("same"=incorrect judgment), although they are no less often correct in their final decision.

To discover whether there are any differences among anxious and normal subjects in the pattern of accuracy and decision-time values as a function of stimulus differences, each subject was rated as to whether he conformed to the pattern characterizing the group as a whole, i. e., increased accuracy and lowered decision time accompanying increased stimulus difference. Although it is conceivable that the mean curves could smooth out individual variations in pattern, possibly anxious subjects might more frequently have irregular sequences of scores. Analysis of individual sequences of scores shows that almost the identical number of

TABLE 6.—*Mean Decision-Time Values for Correct and Incorrect Items, by Stimulus Difference, on Two Occasions of Testing*
(Anxious Patients, N-17; Normals, N-18)

		1 Mm.		2 Mm.		3 Mm.	
Group	Occasion	Correct	Incorrect	Correct	Incorrect	Correct	Incorrect*
Patients	1	4.14	4.23	3.54	4.43	2.43	10.79
	2	3.16	3.57	2.50	4.22	2.25	5.21
Controls	1	3.33	2.85	2.75	2.70	2.31	2.55
	2	2.18	2.52	2.06	2.68	2.00	2.37

*All entries in this column depend on too few cases for reliability.

subjects have the same pattern in each group and on each occasion. Variations from the regular pattern are somewhat commoner in decision time, which generally has greater variability than accuracy scores, but there is no indication that anxious subjects show any greater irregularity or that there is any change between occasions in either group.

Relationship Between Accuracy and Decision Time.—There is considerable reliability between occasions for both scores in both groups; the correlations being both high and significant. For the accuracy values, the product-moment correlation is +0.817 for the normals and +0.769 for the patients. For decision time, the coefficients are +0.804 and +0.857, respectively. It is interesting that, although the mean level of decision time changes considerably more than the mean accuracy values, and more for the patients than for the normals, the degree of correlation is substantially the same for both measures and for both groups. Thus, there is considerable consistency in the ordering of subjects within each group.

To what extent are the accuracy of judgment and the time taken for judgment related? At the outset, it was anticipated that the effect of anxiety on judgmental processes might be seen in these studies in a simultaneous lowering of accuracy and increase in the time required for judgment. Still, it might be equally reasonable to expect that the accurate subject might be slower and that speeding of response would accompany less discriminating judgment. The actual correlations between accuracy and decision time, for each group and on each occasion, show only low and insignificant relationships. For the normals, the correlation between the two variables is +0.170 on the first day and +0.302 on the second day. For the patients, the values are −0.180 and −0.113. Thus, it seems that neither among anxious nor among normal subjects is there any over-all relation between the speed and the accuracy of judgment.

Still, the lack of correlation in either group as a whole might conceal the fact that there are consistent but different individual patterns which taken together sum to minimal correlation. To explore the possibility of individual patterns, correlations were run for each individual of the patient group, using the paired values for the six measures made on the three experimental days. The preexperimental day was excluded because the regular decline in values from this to the first measure of Day 1, noted above, would contribute an artifact to the correlations. The correlations (ρ) ranged from −0.600 to +0.757, approximately half being positive and half negative; but only slightly more than one-third were within the limits ±0.300. Because of the small number of occasions, the reliability of any of these coefficients is questionable, and there is no simple basis on which to judge that the distribution of these values differs from what one would expect in a chance distribution of this number of ρ's. On inspection, however, it does seem possible that there might indeed be two response patterns, one seen in positive, the other in negative, correlation. It may be that for some persons making more accurate decisions involves a slowing of the speed of the decision, while for others reduced speed accompanies greater inaccuracy. Though the present findings are too uncertain to justify such conclusion, they do suggest two patterns of response in this situation.

Comment

The Area Judgment Test requires behavior which is of little general importance to most subjects. The stimuli are intentionally neutral—as such, they have minimal association value—nor is there any immediate or personally relevant consequence of making one or another judgment. The subject is required to distinguish aspects of the stimulus field which are relevant (i. e., squares' size) from those which are irrelevant (i. e., color, position, etc.) and, in terms of this dimension, to designate one of the two items as "larger." The meaning

of "larger" is clear; and from the subject's standpoint all of the evidence necessary for decision is contained within the external, stimulus field. Despite differences in their interpretation of the larger situation, which will soon be discussed, it can be fairly assumed that the motivation in the task is much the same for all—to make judgments correctly, and thus to get "a high score." Thus, the test calls forth "autonomous ego functioning," relatively free from the interference of emotional or unconscious processes. And the evidence over-all is that such functioning could be maintained by most subjects despite rather high levels of anxiety.

It should be noted that the conditions of testing further encourage the ego detachment necessary for judgment in terms of objective stimulus qualities. Lights were dimmed; the room was quieted, and the subject sat with his eyes enclosed by the viewing-box eyepiece. External stimulation was reduced to little more than the two squares which filled the visual field. Similarly, the persons administering the test were intentionally aloof, and communication was limited to little more than giving the test instructions. They existed as part of the test procedure and were intended to have little identity as persons with whom the patient could interact.

Parenthetically, it might be remarked that withal the test was interpreted in strikingly different ways. Possibly because of the apparent simplicity of the procedure and the professionally detached behavior of the examiners, the situation invited the projection of all sorts of meanings. For some, it was a test of sanity, though they could not explain the mechanisms involved. One subject believed that the viewing machine was in fact some sort of camera and in some unknown fashion took pictures of her mind. Others, however, took the procedure at face value—"a test of perception"—and were distinctly relaxed during this part of the experimental day. The behavior of the examiners was felt by some subjects to be cold and rejecting, though others appreciated the cool and competent "going-about-his-business" attitude. Often patients sought warmer and more personal contact. The situation was emotionally threatening when its very simplicity was felt to conceal hidden but ominous meanings, and the subject could not gain reassurance by using accustomed defensive behavior in the social interplay with the examiners.

However, despite evidences of disturbances engendered by the task—noted in the observed behavior of the subject toward the examiners and described in before- and after-interviews—we believe that when they were immersed in the task most subjects could make the required judgments with minimal interference from unconscious or emotional factors.

Consequently, the changes in perceptual functioning between the experimentally defined occasions were rather small. On only one day is there a significant change for the group as a whole. However, when the data are regrouped in terms of the degree of emotional response to the stress interview, there tends to be more consistent changes in perceptual performance. Thus, we feel that, while the imposed stress and the affect aroused by it had a discernible effect in reducing the accuracy of the perceptual judgments, these effects were generally rather small, perhaps partly because the anxiety evoked by the situation was rarely very great and partly because the task and test situation allowed for segregating the perceptual decision from disrupting emotional factors.

We have sought to describe the relations between affective and perceptual behavior in two types of comparisons: (*a*) between occasions of greater and lesser stress, and as correlated with emotional changes, within the anxious patient group; and (*b*) by contrasting the performance of the anxious patient with that of normal subjects on two nonstress occasions. It is rather interesting that the dimension of the test which varies is different in the two comparisons: (*a*)

Within the patient group such differences as are found are mainly in the accuracy scores, with little evidence of systematic changes in decision time; and (*b*) by contrast, the major differences between patients and normals are in the patterning of time scores, with virtually no difference in accuracy. In the simplest view, it might be assumed that if one or the other dimension varied more with anxiety it would be similarly seen in both comparisons; that each varies on one of the comparisons but not in both would seem paradoxical.

While schematically both cases imply contrast in the levels of anxiety, there are obvious and important differences between them. The patients differ from the normals not only in being more anxious but, as importantly, in terms of enduring aspects of personality organization, including defenses and modes of handling potentially threatening situations, which have been integrated over years. Similarly, the interpretation of the task and motivation in it, as well as the definition of the social situation generally, might well differ considerably between the groups. By contrast, testing the same patients on a number of occasions abstracts the relatively smaller changes in free anxiety which can be aroused by the experimental situation, and of necessity rules out the more enduring aspects of personality organization as a primary source of variation.

Patients, we have noted, tend to be generally slower in making the perceptual decisions than the normal controls. This is particularly true when the items cannot be distinguished and when they are in fact minimally different in size. It would seem that the anxious subject has greater difficulty in resolving the conflict of deciding between the almost equal squares, although, as we have also noted, the decision finally reached is no less often correct. Whether this slowing reflects greater hesitancy in admitting inability to discriminate, or whether it directly indicates greater difficulty in discrimination itself, we cannot say. It may also be true that despite the identical test instructions given all subjects, the patients and the normals differed somewhat in their interpretation of the requirements of the task. The patients may have set themselves to be as accurate as possible, regardless of time taken, while the normals sought to be quick as well as accurate. There is little question that implicit sets established by the subjects, as well as explicit sets imposed by the experimental task, can produce differences as great as or greater than those found in this study. Clearly, however, we do not have evidence here for deciding among alternate interpretations of these findings.

However, whatever determines the anxious patient's slower response, we have seen that it does not vary in any sensible way as he becomes further disturbed by the stress interviews. Instead, the accuracy of judgment changes, particularly on those occasions when the greatest emotional disturbance is aroused. Without using more time, the patient more frequently reaches the decision that the squares do not differ in size. At these heightened levels of anxiety, it does appear that the patients are less able to distinguish the relevant dimensions of the square and that there is a reduction in the adequacy of perceptual performance. In some cases, as we shall discuss again later, the mechanism seems to involve an inability to sustain the tension necessary for making decisions, and the response "same" arises from the need to escape the requirements of the task.

One finding deserves special comment. The correlation between change in accuracy scores and the increase in emotional disturbance from before to after the stress interview tends to be positive on the first experimental day and then increasingly negative on the two succeeding days. Separate analysis [5] has shown the stress interview to be generally least effective in arousing anxiety on the first day; and, considered against this lower level, increased affect leads to the *facilitation* of perform-

ance. By contrast, on the generally more stressful days, still further rise in affect leads to *interference* with performance. These findings support the general view that the relation between anxiety and performance over a sufficiently large range is not linear, but, rather, curvilinear, and give further evidence that moderate amounts of anxiety may organize rather than disrupt behavior.[6]

For the group as a whole, there is little indication of relationship between accuracy and time, either found in correlation within patients or normals or, as just discussed, to be seen in coordinate changes of the two variables under stress. But when each patient is considered individually, there is indication of two distinct patterns of accuracy-time relationship found in the changes between occasions. Although the data are not conclusive, it appears that for some subjects accuracy and decision time are positively related (when they are more accurate, their judgments are made more rapidly, and, conversely, slowing down goes with less accurate judgments), while for other patients there is a negative relationship (they are most accurate when slowest, least accurate when fastest). From the evidence on hand, we are uncertain how definite these particular patterns are, or to what they may be related.

There is little question, however, that persons differ greatly in the ways in which they dealt with the problem posed by the test. Though not represented in the quantitative analyses of the patterns of scores, observation of the behavior of patients during testing and clinical review of all the test data for each subject separately indicate rather distinct and consistent modes of decision making, which may well be related to more general personality characteristics. Some subjects pondered each of the stimulus pairs carefully and slowly, and under stress became even more deliberate and compulsive in considering all possible cues before announcing a decision. For some, rapidity of judgment seemed to go with a genuine decisiveness, but for others equally rapid judgments apparently served the primary purpose of relieving the subject of the need for making the judgment.

Running through a number of these individual behaviors, there is, we feel, a personality characteristic of rather general importance—the ability to tolerate the tension aroused by having to make a decision. Conflict is inherent in any judgment involving alternate and exclusive choices, and tension is necessarily aroused, which is then resolved when the judgment is made. Some of our anxious patients were visibly unable to maintain this tension and would consequently give very rapid responses in order to escape it. Their need apparently was to get the problem over with, rather than to reach the best solution. We have noted similar behavior in another decision-making situation.[4] At the other extreme were persons who delayed excessively in rendering a final decision. Such persons are apparently better able to tolerate the immediate task-engendered tension than run the risk of committing themselves to a definite position. For them, the ultimate outcome of taking a stand is far more threatening than the existing discomfort of not deciding. Thus most of the time is not applied in a constructive solution of the problem at hand, but reflects an obsessional process of warding off the potentially graver consequences of the decision itself.

The data of these studies call attention to some of the number of possible individually organized patterns of judgmental behavior, which taken together might attenuate any group differences of the sort discussed earlier. Clearly, such patterns, as related to more general aspects of personality organization, should be considered in their own right, as in the recent study by Block and Peterson.[7]

Summary

To study the relationship between anxiety and perceptual functioning, measured in the accuracy and speed of size discrimi-

nation, 19 anxiety-prone patients were tested once on a preexperimental day and twice (before and after a stress interview) on each of the three subsequent days. For comparison, a group of 18 normal, hospital employees were tested on two occasions. Forty-five pairs of squares, differing in size as well as in other stimulus attributes, were presented in a different order on each occasion with the request that the subject identify, if he could, the larger member in each pair.

For the group as a whole there is little evidence of much change in test performance, particularly in decision-time scores, in response to the stress interview. On only one of the three experimental days is there a significant drop in poststress accuracy values. However, when the days are regrouped in terms of the amount of emotional disturbance engendered by the interview, there is somewhat more evidence of stress effects: Generally, on the occasions of the largest stress-produced increases in affect there is the greatest drop in accuracy, the least change in accuracy values occurring on the days of smallest affect increases.

However, there is little direct relation between over-all emotional levels, based on ratings made over the four days, and test performance. More distinct relationship emerges, however, when correlations are run between the pre- to poststress changes in affects and the changes in test performance on each of the experimental days. On the first day, subjects who become most disturbed by the stress interview tend to be more accurate and somewhat slower in their judgments; on the second day increased affective disturbance is paralleled by decreased accuracy and speeding of response, and on the third day, by both decreased accuracy and slowing of response. This change from positive to negative correlation (in accuracy scores) from the less disturbed to the more disturbed days gives some indication of what is believed to be a generally curvilinear relation between anxiety and performance: At more moderate levels, increased anxiety facilitates, at higher levels similar increase disrupts, performance.

Of the two measures, accuracy is found to be more distinctly related to the stress and affective changes within the patient group; but, interestingly, the major differences between the patients and the normals are found in the decision-time measure. On each of the two comparison occasions, the patients and the normals are virtually identical in accuracy, though the patients are decidedly slower, particularly on the first day. Generally, the patients seem to have greater difficulty in resolving the judgmental conflict, more particularly so when the stimulus items were actually minimally different or when the decision of "no difference" had to be reached or admitted. Within neither group as a whole is there correlation between accuracy and decision time. There are, however, suggestions of individual patterns, which are discussed as possibly related to more general and personally consistent modes of judging and resolving conflict, reflecting perhaps differences in the ability to tolerate the tension aroused by having to decide between alternate possibilities.

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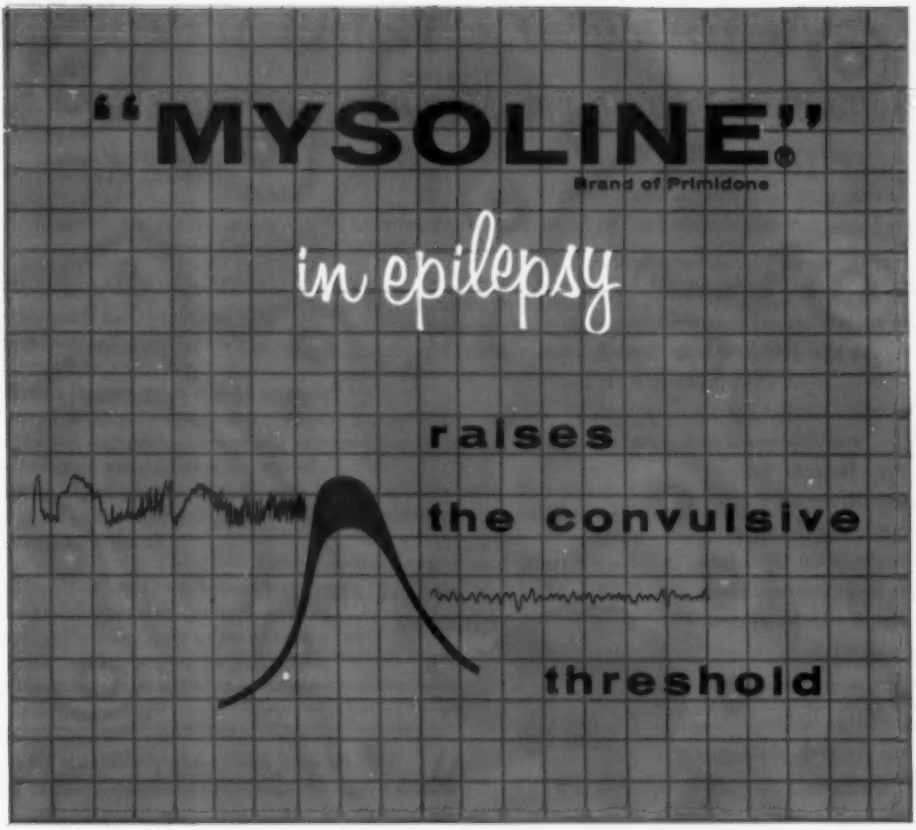

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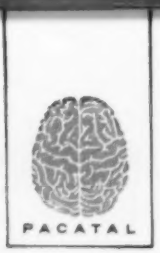

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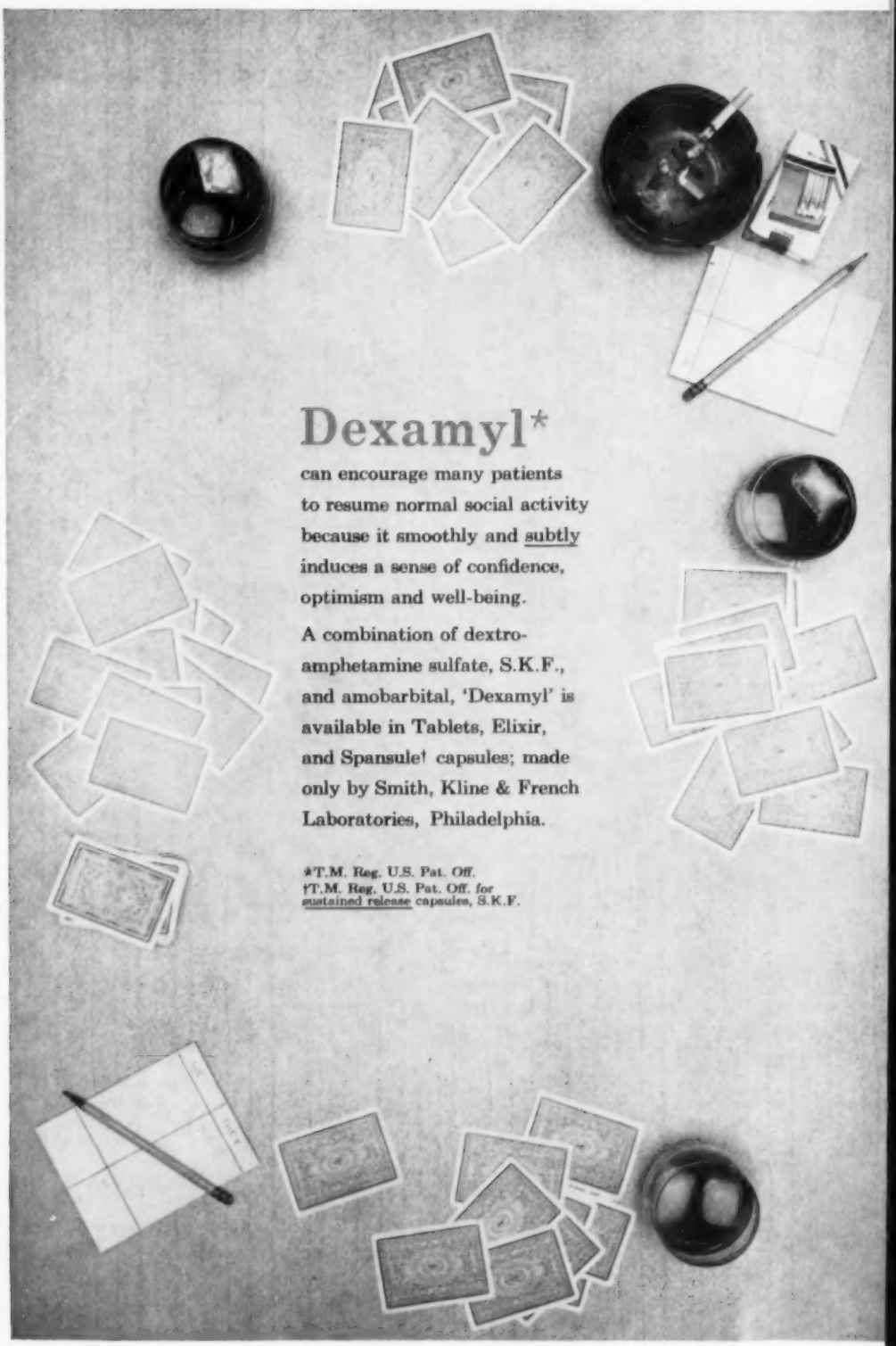

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